MINISTERNOTOMY AORTIC VALVE REPLACEMENT DECREASES THE NEED FOR BLOOD TRANSFUSION AND IMPROVES CLINICAL OUTCOMES IN COMPARISON TO CONVENTIONAL FULL STERNOTOMY APPROACH

by

Najah Adreak

MD, The University of Tripoli, 2009

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Surgery)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

December 2020

The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, the thesis entitled:

Ministernotomy approach for aortic valve replacement decreases the need for blood transfusion and improves clinical outcomes in comparison to conventional full sternotomy approach

submitted by Najah Adreak in partial fulfillment of the requirements for

the degree of Master of Science

in Surgery

Examining Committee:

Dr. Anson Cheung, Departments of Surgery and Biochemistry & Molecular Biology, UBC
Supervisor

Dr. Bruce MacManus, Department of Pathology and Laboratory Medicine, UBC
Supervisory Committee Member

Dr. Samuel Lichtenstein, Department of Surgery, Division of Cardiothoracic Surgery, UBC
Supervisory Committee Member

Dr. Richard Cook, Department of Surgery, Division of Cardiothoracic Surgery, UBC
Supervisory Committee Member

Abstract

Background: Advantages of mini-sternotomy aortic valve replacement (MSAVR) including improved cosmesis, reduction in postoperative pain, blood loss, shorter length of hospital stay (LOS) and better wound healing. However, MSAVR is not widely adopted by surgeons and clinical outcomes of MSAVR have not been reported in Canada. We study the outcomes of MSAVR in our institution in British Columbia (BC) comparing to full sternotomy aortic valve replacement (FSAVR).

Methods: Retrospective analysis of Cardiac Service BC database to evaluate all isolated aortic valve replacement (AVR) performed in our institution from Jan 2007 to Dec 2016. Nine hundred and ten patients were identified (776 FSAVR and 134 MSAVR) with a median follow-up period of 6.2 years. Standard statistical analysis was conducted.

Results: Baseline variables between the two groups were similar with a mean age of 70 years and 40% were females. 77.5% of MSAVR patients were in NYHA III/IV vs 49.3% (p=<0.001) and had a greater incidence of renal failure (12.7% vs 8.8%, p=0.15). Bioprosthetic valve implanted in more than 90 % of cases. The freedom from blood product transfusion in the MSAVR group was significantly higher than FSAVR **(**65.7% vs 49.6 % respectively, p= <0.001). The CBP and AXT times were approximately 9 and 6 minutes shorter in the MSAVR group than FSAVR, respectively (mean CBP 75.4 ± 14.7 vs 84.3 ± 30.0, p=0.014, and mean AXT 58.5 ± 12.2 vs 64.7 ± 24.7, p=0.08, respectively). There were no significant differences in the incidence of new onset of atrial arrythmias and renal dysfunction. There was no significant difference in 30-day (p=0.79) and long-term mortality between groups (p=0.70). LOS in the hospital was shorter in the MSAVR group (mean 7.8 ± 6.2 vs 8.6 ± 7.2, p=0.006).

Conclusion: We have validated that mini sternotomy is an effective alternative to the standard approach for aortic valve replacement. It is proven to be a safe and effective treatment for aortic stenosis with decrease in blood product transfusion rate, and hospital stay with equivalent 30-day mortality and long-term survival rate. It should be considered as part of the armamentarium of cardiac surgeons in the modern era.

Lay Summary

Background: A diseased aortic valve is fetal and needs surgery. The standard surgery is done by cutting all the breastbone to replace the valve. This causes a painful incision and is particularly risky in older patients with multiple health issues. The proposed surgical technique uses only a small cut in the breastbone to replace the damaged valve.

Question: Does the smaller cut procedure to replace the aortic valve have similar outcomes to the full incision approach?

Method: We studied the database to compare isolated aortic valve replacement done in our center for ten years.

Result: No increase in death risk, the occurrence of abnormal heart rhythms or kidney problems between the two approaches. Small-cut surgery patients went home earlier and took fewer blood products.

Conclusion: The smaller incision surgery is a safe and effective treatment for aortic stenosis without any increase in the risk of death or other major complications.

Preface

This dissertation is original and unpublished by the author Najah Adreak. Under my supervisor guidance, Dr. Anson Cheung, I developed the idea, drafted the protocol, undertook the literature review, obtained the ethic review, obtained data from cardiac service BC data registry and did chart review for missing data, cleaning the data and writing. The analyse of data was done with the great help of Dr. Defen Peng, the statistician of this research. All of the work presented in this paper was conducted at St. Paul's Hospital, Division of Cardiovascular and Thoracic Surgery, Department of Surgery, University of British Columbia (UBC). The study was approved by the St. Paul's Hospital and University of British Columbia Institutional Review Board (CREB) (certificate # H17-00965).

This manuscript presents the final and approved results of the project. A poster was presented at the Canadian Cardiovascular Congress 2019, (**Najah Adreak**, Defen Peng, Yinshan Zhao, Anson Cheung :The short- and long-term survival rate in mini-sternotomy AVR is equivalent to those of full sternotomy AVR: BC experience) and an oral presentation was made at the 25th Chung Surgery Research day (**Najah Adreak**, Defen Peng, Yinshan Zhao, Bruce MacManus, Anson Cheung: Short- and long-term survival rates of mini sternotomy vs full sternotomy aortic valve replacement at St. Paul's hospital, the, the University of British Columbia)

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AS	Aortic Stenosis
AR	Aortic Regurgitation
AVR	Aortic Valve Replacement
AVA	AV Orifice Area
AF	Atrial Fibrillation
ACE	Angiotensin-Converting Enzyme I
CABG	Coronary Artery Bypass Grafting
FAVR	Full Sternotomy Aortic Valve Replacement
LVEF	LV Ejection Fraction
LV	Left Ventricle
MIAVR	Mini Invasive Aortic Valve Replacement
MSAVR	Mini-Sternotomy Aortic Valve Replacement
NYHA	New York Heart Association
SCTS	Society of Cardio-Thoracic Surgery
TAVI	Transcatheter Aortic Valve Implantation

.

Glossary

Length of hospital stay	The time spent in hospital from surgery day to discharge
Lowest eGFR	Lowest estimated glomerular filtration rate during the postoperative period until discharge
New onset atrial fibrillation	Atrial fibrillation that began in the postoperative period without any indication of pre-existing atrial fibrillation
Obesity	Body mass index > 30 kg/m2
Prolonged cardiopulmonary bypass	Length of cardiopulmonary bypass > 80-minutes
Postoperative blood transfusion	Total amount of blood received during the hospital stay, including units that were transfused during surgery
Renal dysfunction	An estimated glomerular filtration rate ≤ 15 eGFR <60 - mL/min/1.73m2 for an acute period of time within the postoperative period with a full and steady return to the normal range
Renal failure	Sustained estimated glomerular filtration rate <15 mL/min/1.73m2, or acute on chronic renal failure

Acknowledgements

I would like to offer my gratitude to my supervisor, Dr. Anson Cheung, who masterfully and patiently orchestrated many steps of this research and guided me along the way. I am also grateful to Dr. Cheung for providing me with opportunities for professional development and advancing my career. I truly appreciate and value everything I have learned from you. You will forever remain a significant contributor to my success and achievements.

I would also like to thank Dr. Defen Peng and Dr. Yinshan Zhao, who provided much support and feedback with the statistical aspect of this thesis, especially Dr. Peng, who always goes above and beyond. Also, I would like to thank my supervisory committee, Dr. Bruce MacManus, Dr. Samuel Lichtenstein, for their support and guidance on this project.

I also offer my gratitude to Dr. Lillian Ding and the cardiac service BC data registry team for helping with data collection. The data obtaining process was very challenging, and they did all the best to help me out. A special thanks to the program director Dr. Alice Mui for her help and support over the course of the program. I am also grateful to my friends and MSc colleagues who always provide me with their support and help.

Lastly, special thanks to my parents, my father (who passed away while I am here), and my family. A special feeling of gratitude to my loving mother, Mubarak Nass, my hero, for her endless love and support throughout my life. She has never failed to guide me and motivate me. She has shown me the value of faith and dedication by being the most outstanding example of that. I attribute all my success in life to the moral, intellectual and education I received from her. Thank you for giving me the strength to reach for the stars and chase my dreams. My sisters and brothers deserve my wholehearted thanks as well.

Also, I am grateful for my homestay family, who accepted me as a part of their family. Through thick and thin, they generously and unconditionally expressed their love and support, and kindly shared their time with me and helped me survive being away from my family.

I would like to thank my sponsoring institution, the Libyan Ministry of health, and my country, Libya, for giving me this opportunity by financially supporting my education throughout the program.

Dedication

I dedicate this work to my mother, my father (in heaven), my family, and all patients we (as HCP) strive to provide the best care for them through research and innovation.

Chapter 1: Background

1.1 Heart Anatomy

The heart is located in the middle of the thoracic cavity, in a space called the mediastinum between the lungs and their pleural covering. The heart lies posterior to the sternum (breastbone) and the rib cage and rests on the superior surface of the diaphragm. The heart is covered by a membrane called the pericardium, which contains pericardial fluid.

The heart is a muscular pump that serves two functions: (1) to collect deoxygenated blood from the tissues of the body and pumps it through the lungs to pick up oxygen and to release carbon dioxide, and (2) to collect oxygenated blood from the lungs and delivers to the body. The heart is composed of four chambers, the upper two chambers are called the right and left atrium, and the lower chambers are the right and left ventricle. The right side is responsible for collecting deoxygenated blood and pumping it to the lungs. The left side is responsible for collecting oxygenated blood from the lungs and delivering it to body tissues.

The blood flow in the heart is unidirectional, where blood travels from the atria to the ventricles. Blood flow is guided by the atrioventricular valves between the atria and ventricles, the mitral and tricuspid valves, on the left and right side, respectively. Blood flow between the heart and the great vessels (aorta and pulmonary artery) is guided by semilunar valves, the aortic valve between the left ventricle and aorta and the pulmonary valve between the right ventricle and pulmonary artery. (Fig 1) The blood supply of the heart comes from coronary arteries, which originate from the ascending aorta. In this thesis, I will focus on aortic valve anatomy and aortic valve disease.(1)

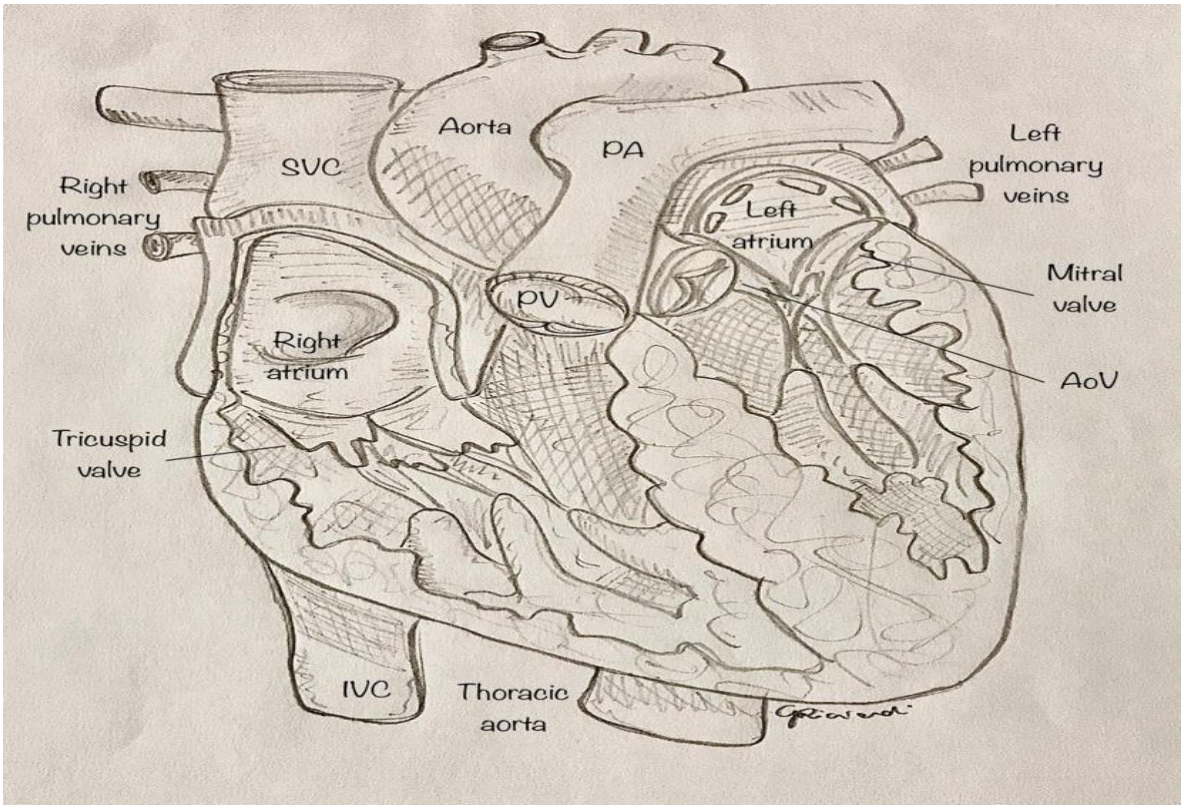

Figure 1. The heart anatomy, anterior view. This cartoon shows the heart chambers, valves and great vessels. (Hand drawing by Gabriella Ricciardi, cardiac surgery resident from Italy.)

1.2 Aortic valve

The aortic valve (AV) separates the terminal portion of the left ventricle outflow tract (LVOT) from the aorta. The normal AV consists of three semilunar leaflets or cusps projecting outward and upward into the lumen of the ascending aorta (Fig 2).

The sinuses of Valsalva are spaces between the free edge of each leaflet and the points of attachment to the aorta. Two of the three sinuses are named by the adjacent coronary ostia, the right and left coronary sinuses, while the third is called a non-coronary sinus. The leaflets are separated from one another at the aorta by the right/left right/non-coronary and left/non-coronary commissures (Fig 2). The area around the left/non-coronary commissure is the fibrous continuity,

which connects the aorta and the mitral valve annulus. The area below the left non-coronary commissure is the aorto-mitral curtain, which is an anatomical landmark for root enlargement procedures. The right non-coronary commissure is positioned directly above the penetrating atrioventricular bundle and membranous septum. The right and left commissure oppose the posterior commissure of the pulmonary valve, and the two associated aortic cusps oppose the right ventricular infundibulum. The only part of the AV that is not closely related to another cardiac chamber is the lateral part of the left coronary sinus and in a direct relationship with the free pericardial space. The AV leaflets meet at the center along a line of coaptation. At the center of each leaflet, there is a thickened nodule named the nodules of Arantius.

Given the semilunar shape of the leaflets, the AV does not have a ring-shaped annulus. Instead, the leaflets have semilunar attachments along with a hollow cylinder or cuff of tissue interconnecting the left ventricular (LV) and the proximal aorta (Fig 2). The distal border of the cuff is the sinotubular junction, which connects the commissures by imaginary lines. In comparison, the proximal border is the ventriculoarterial (VA) junction, which has both hemodynamic and anatomic parts. The hemodynamic VA junction is marked by the semilunar attachments of the leaflets. In contrast, the anatomic VA junction is marked by the circular attachment of the proximal aorta and the muscular and membranous ventricular septum.(2)

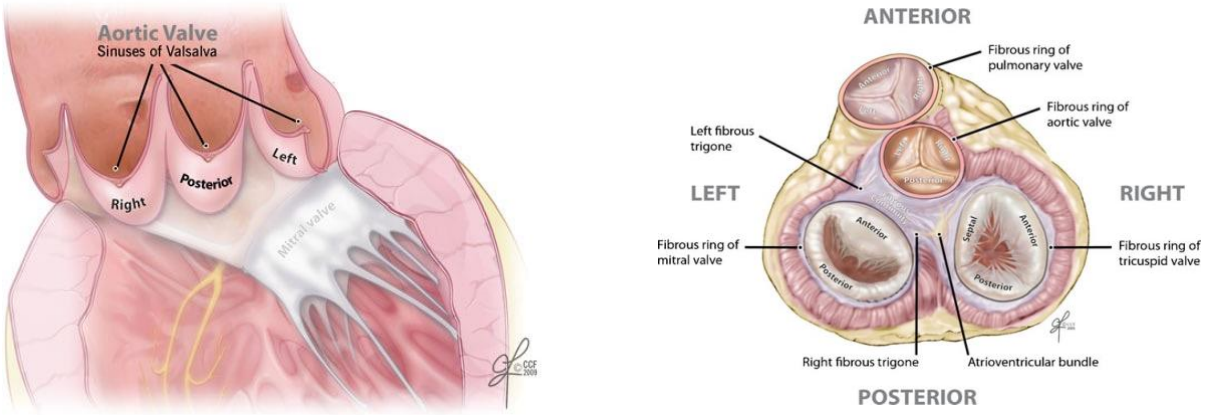

Figure 2. Anatomical relationship between the aortic valve leaflets and surrounding structures. (Reproduced with permission from the Cleveland Clinic, Cleveland, OH.)

1.3 Aortic valve stenosis

The aortic valve stenosis (AS) happens when the valve becomes fibrotic or calcified with incomplete opening. In healthy subject, adult human aortic valve area is measured around 3 to 4 cm^2. The clinical manifestation of AS depends on the severity of the narrowing. There are many causes of AS, including congenital, rheumatic, degenerative and inflammatory

1.3.1 Prevalence

Aortic valve stenosis is the most prevalent valvular heart disease, affecting approximately 1% of the adult population in the US and comprises a range of linked pathologies, including senile degeneration and functional regurgitation.(3) The most common causes of AS are the acquired degenerative disease, congenital bicuspid AV and rheumatic heart disease. As ageing is one of the risk factors for AS, the prevalence rises exponentially with age affecting more than 1 in 50 adults over 75 years.(4) As a result, senile or degenerative AS is the leading cause of aortic valve disease in developed countries. Rheumatic heart disease remains the most common cause of aortic

valve disorder in the less developed part of the world and yet it still constitutes 22% of valvular heart disease in Europe.(5)

1.3.2 Senile aortic stenosis

The most common cause of AS is degenerative calcification of the AV, which typically occurs in septuagenarians and octogenarians. Throughout life, continuous deposition of calcium (Ca) starting at the flexion lines of leaflet bases, leading to restricted mobility of the cusps. This calcification can extend deep into the aortic annulus. Ca deposits may involve the sinuses of Valsalva and the ascending aorta. The wear and tear of mechanical stress on an otherwise healthy valve induces proliferative and inflammatory reactions with lipid deposition, upregulation of angiotensin-converting enzyme (ACE) activity, infiltration of macrophages and T lymphocytes in a process similar to atherosclerosis. Needless to say, risk factors for the development of calcific AS are also similar to those for atherosclerosis and including elevated serum levels of low-density lipoprotein (LDL) cholesterol, diabetes mellitus, smoking, and hypertension. Therefore, coronary artery disease is commonly present in patients with AS. Age-related AV sclerosis is associated with an increased risk of cardiovascular death and myocardial infarction (MI).

Due to the calcific nature of senile AS, it is also observed in several other conditions that characterized by increase in calcium deposition, such as Paget's disease of bone and end-stage renal disease.(2)

1.3.3 Pathophysiology of aortic stenosis

The pathophysiological effect of AS on the heart depends on the degree and duration of valvular stenosis. In the beginning, it causes a little effect on the hemodynamic. While the valve area is reduced from the normal range of 3-4 cm^2 to 1.5 to 2 cm^2, at this point, hemodynamically significant obstruction of LV outflow develops with a concomitant increase in LV pressure and

lengthening of the LV ejection time. The rise in LV pressure increases wall stress and leads to LV hypertrophy (LVH).

As the LV hypertrophies, it becomes less compliant, and LV end-diastolic pressure (LVEDP) increases without LV dilatation. As a result, diastolic dysfunction occurs, and the ventricle becomes increasingly dependent on atrial systole for filling. This explains the exaggeration of symptoms with the development of atrial arrhythmia.(1, 2)

LVH has other adverse negative consequences for the heart. LVH increases systolic pressure and prolongs ejection time, which contributes to an increase in myocardial oxygen consumption. Increased diastolic pressure with decreased diastolic time increases endocardial compression of the coronary arteries, reducing coronary flow reserve and therefore reduced myocardial perfusion time. The increased demand of the hypertrophied ventricle and decreased delivery capacity can cause subendocardial ischemia, especially during exercise. Anginal symptoms can occur along with LV dysfunction. Severe LVH can be reversed to a certain degree by aortic valve replacement (AVR) and is associated with decreased long-term survival even after successful surgery. As a consequence of long-lasting severe AS, the LV may decompensate, leading to dilated cardiomyopathy and heart failure. With cardiac output further decreases, pulmonary hypertension may be evidenced.(2, 6) The severity of AS can be graded by the AV orifice area (AVA), mean pressure gradient and peak jet velocity across the valve.

1.3.4 Clinical presentation

The typical symptoms of AS are angina pectoris, syncope and symptoms of congestive heart failure (CHF) (dyspnea, orthopnea and paroxysmal nocturnal dyspnea). Patients may commonly present with less specific symptoms such as fatigue and decreased exercise tolerance. Another presentation of AS is gastrointestinal bleeding secondary to angiodysplasia in the colon, small

bowel and stomach. In advanced AS, atrial fibrillation and pulmonary hypertension can develop. In patients with AS, there is an increased risk of developing infective endocarditis. The presence of symptoms is a crucial indicator of long-term mortality and morbidity.(7) Sudden death in asymptomatic AS patients can occur at an estimated rate of 1% per year.

With the onset of symptoms, survival is dramatically reduced without surgical intervention. The median survival for patients with angina is 5 years, and for those with syncope, it further reduces to 3 years and 2 years for patients with CHF. (Fig 3)(8)

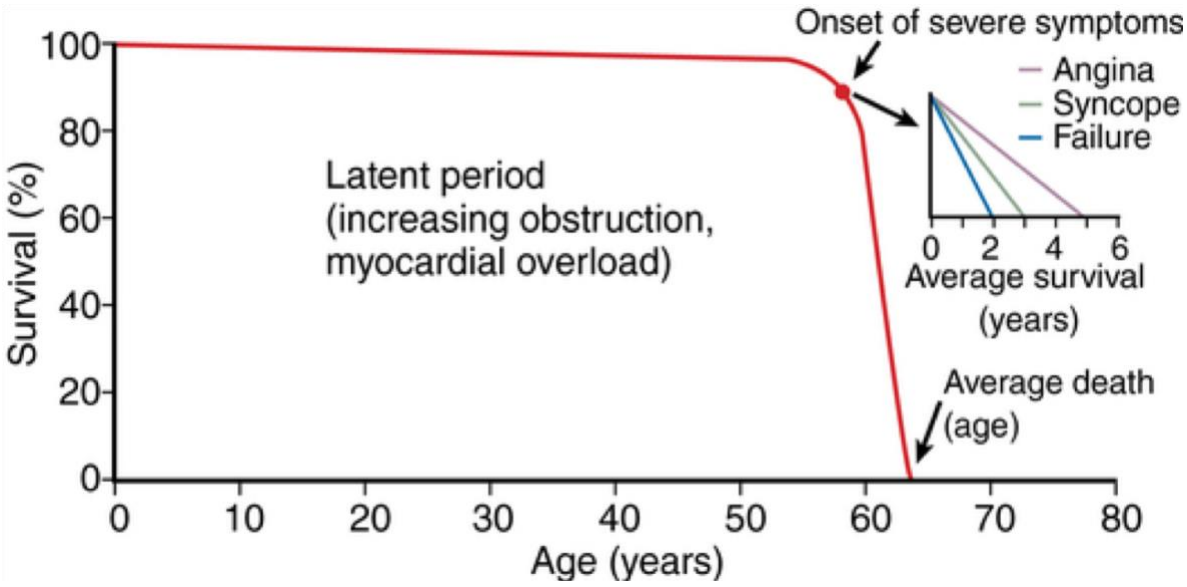

Figure 3. Natural history of aortic stenosis. After a latent period of gradually increasing valvular stenosis and left ventricular pressure overload, the onset of symptoms heralds an ominous outcome with >50% of patients succumbing over the next 2 to 3 years. Modified from Ross and Braunwald.

The severity of symptoms correlates with the degree of valve stenosis. The degree of aortic valve stenosis is generally classified into mild, moderate and severe. Severe AS is usually defined as a mean gradient >40 mmHg, AVA <1 cm^2 and peak aortic jet velocity >4.0 m/s. (Table 1)

Severe AS is a fatal condition if left untreated, three-quarters of patients will die within three years of symptom onset.(8) However, even with the absence of symptoms, severe aortic valve disease has a poor prognosis. Evidence from the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) Study, 10% of patients with mild or 38% with moderate AS progressed to surgically significant disease within five years.(9)

Table 1. Classification of Aortic Stenosis Severity

Indicator	Mild	Moderate	Severe
Aortic valve area (cm^2)	>1.5	1.0 - 1.5	<1.0
Aortic valve area index (cm^2 per m^2)	>0.85	0.60 - 0.85	<0.6
Mean pressure gradient (mm Hg)	<20	20 - 40	>40
Peak jet velocity (m/sec)	<3.0	3.0 - 4.0	>4.0

Adapted from Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, et al: 2008

Clinical signs of AS include systolic crescendo-decrescendo murmur best heard at the right upper sternal border, delay second heart sound from the prolongation of systolic ejection time and single or paradoxical splitting of heart sounds. In severe or decompensated AS patients, a classic pulsus parvus (small pulse) occurs due to decreasing stroke volume and falling in systolic and pulse pressures. LVH is evident as a sustained apical thrust or heave. When hypertrophied heart dilates, the apical impulse can be displaced. Other physical findings of advanced AS including a

prominent atrial kick and prominence of the jugular venous wave secondary to decreased right ventricular compliance caused by right ventricular hypertrophy.(10)

1.4 Management of aortic stenosis

Patients with aortic valve stenosis may not seek medical care until the onset of symptoms. Patients with no or mild symptoms may benefit from medical therapy. However, when symptoms become severe, surgical intervention is indicated.

1.4.1 Medical management of aortic valve stenosis

Patients with symptomatic AS require immediate medical care to control their symptoms. Lipid-lowering, antihypertensive, congestive heart failure and anticalcific agents have been studied. Symptoms of congestive heart failure can be controlled by a diuretic. However, beta-blockers and vasodilators should be avoided as the former decreases cardiac output or while the latter causes hypotension and may decrease coronary perfusion.

However, a recent review done by Marquis-Gravel and his colleagues has proven that medical therapy has no role in reducing AS progression or improving prognosis.(11) The current American Heart Association/American College of Cardiology guidelines do not provide any recommendations on pharmacological treatment for AS, except for controlling concomitant hypertension. Prophylactic antibiotics are recommended before any dental or surgical procedures for infective endocarditis.(12, 13)

Percutaneous balloon valvuloplasty is effective in congenital AS in selected young patients. However, the procedure's durability is limited with early valve re-stenosis and does not affect long-term survival. In selected cases, valvuloplasty should be considered a bridge to surgical, transcatheter intervention, or palliative management.(12, 13)

1.4.2 Surgical management of aortic valve stenosis

The only proven and recommended management for symptomatic AS is AVR, either surgically or recently by catheter-based technology. Either approach has demonstrated improvement in long-term survival in patients with AS.(12, 13)As the presence of symptoms is the primary indication for AVR in AS patients, AVR's benefit in asymptomatic patients is still unclear. Current guidelines recommend AVR for patients with symptomatic AS, patients with asymptomatic moderate or severe AS who also require coronary revascularization or surgery of the aorta and patients with severe AS with reduced ejection fraction (EF). (Table 2)

A potential benefit of AVR in asymptomatic patients has been studied recently. In those studies, propensity-matched cohorts of asymptomatic patients with severe AS who underwent AVR had significantly improved survival. LVH is responsible for reduced survival and can be reversed partly by AVR.

Table 2. Recommendations for intervention in patients with severe AS (ESC/EACTS guidelines 2017)

Recommendations	COR	LOE	References
AVR is recommended for symptomatic patients with severe high-gradient AS who have symptoms by history or on exercise testing (stage D1)	I	B	9,91,134,135
AVR is recommended for asymptomatic patients with severe AS (stage C2) and LVEF <50%	I	B	136,137
AVR is indicated for patients with severe AS (stage C or D) when undergoing other cardiac surgery	I	B	108,138
AVR is reasonable for asymptomatic patients with very severe AS (stage C1, aortic velocity ≥5.0 m/s) and low surgical risk	IIa	B	139,140
AVR is reasonable in asymptomatic patients (stage C1) with severe AS and decreased exercise tolerance or an exercise fall in BP	IIa	B	25,47
AVR is reasonable in symptomatic patients with low-flow/low-gradient severe AS with reduced LVEF (stage D2) with a low-dose dobutamine stress study that shows an aortic velocity ≥4.0 m/s (or mean pressure gradient ≥40 mm Hg) with a valve area ≤1.0 cm^2 at any dobutamine dose	IIa	B	43,141,142
AVR is reasonable in symptomatic patients who have low-flow/low-gradient severe AS (stage D3) who are normotensive and have an LVEF ≥50% if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms	IIa	C	N/A
AVR is reasonable for patients with moderate AS (stage B) (aortic velocity 3.0–3.9 m/s) who are undergoing other cardiac surgery	IIa	C	N/A
AVR may be considered for asymptomatic patients with severe AS (stage C1) and rapid disease progression and low surgical risk	IIb	C	N/A

AS indicates aortic stenosis; AVR, aortic valve replacement by either surgical or transcatheter approach; BP, blood pressure; COR, Class of Recommendation; LOE, Level of Evidence; LVEF, left ventricular ejection fraction; and N/A, not applicable.

AVR through a full median sternotomy is the standard gold treatment for symptomatic AS. This approach involves an incision that extends from the sternal notch to the xiphoid by dividing the entire sternum longitudinally. The full median sternotomy approach provides the surgeon with full exposure to all cardiac structures. The 5-year survival of median full sternotomy AVR is 83% in the United Kingdom, and the in-hospital mortality is 1.49%.(14) The Society of Thoracic Surgeons reported a hospital mortality rate of 2.6% and stroke risk of 1.4% following isolated AVR.(15)

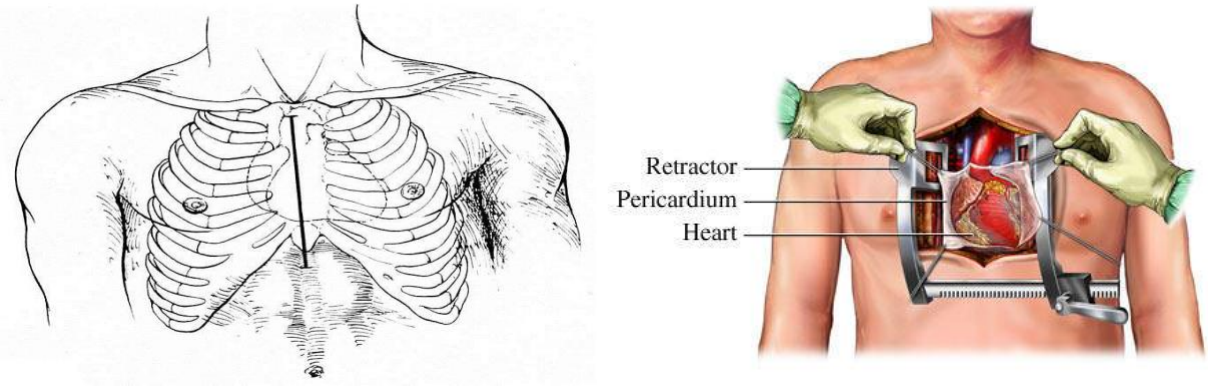

Figure 4. Median sternotomy incision. These two diagrams show the median sternotomy incision, where the sternal bone is opened completely. The incision is extended from sternal notch to xiphoid process.

1.4.3 Full sternotomy and ministernotomy surgical approaches for aortic valve replacement

As a result of the increasing proportion of elderly with multiple comorbidities with AS, the standard approach has a higher operative risk in patient over 75 years and many were under-referred or denied surgical intervention. The primary aim of minimally invasive approach is to

reduce the invasiveness of AVR, while preserving the excellent surgical outcome of the standard approach. In 1993, Rao and Kumar were the first to describe AVR through a right anterior thoracotomy.(16) Cosgrove and Sabik used the term “minimally invasive" to describe AVR via a 10-cm right parasternal incision, excising the second and third costal cartilages and utilizing femoral cannulation to establish cardiopulmonary bypass (CPB).(17) With the absence of retraction and stress placed on the sternum, patients reported reduction in pain and were able to return to their normal activities earlier. Although this approach has largely been abandoned due to the late complication of lung herniation and ribs instability. These results served as catalyst for minimally invasive open-heart surgery.

By definition, minimally invasive aortic valve replacement (MIAVR) is any AVR not performed with a full sternotomy and CPB support by STS database definition. The only procedure that fits this definition is transcatheter aortic valve implantation (TAVI).(18) This definition has been revised by the American Heart Association to describe MIAVR as "...small chest incision that does not include full sternotomy".(19) Mini-sternotomy and mini-thoracotomy approaches were most commonly used for AVR and the former is by far the most predominant. (Fig 5)

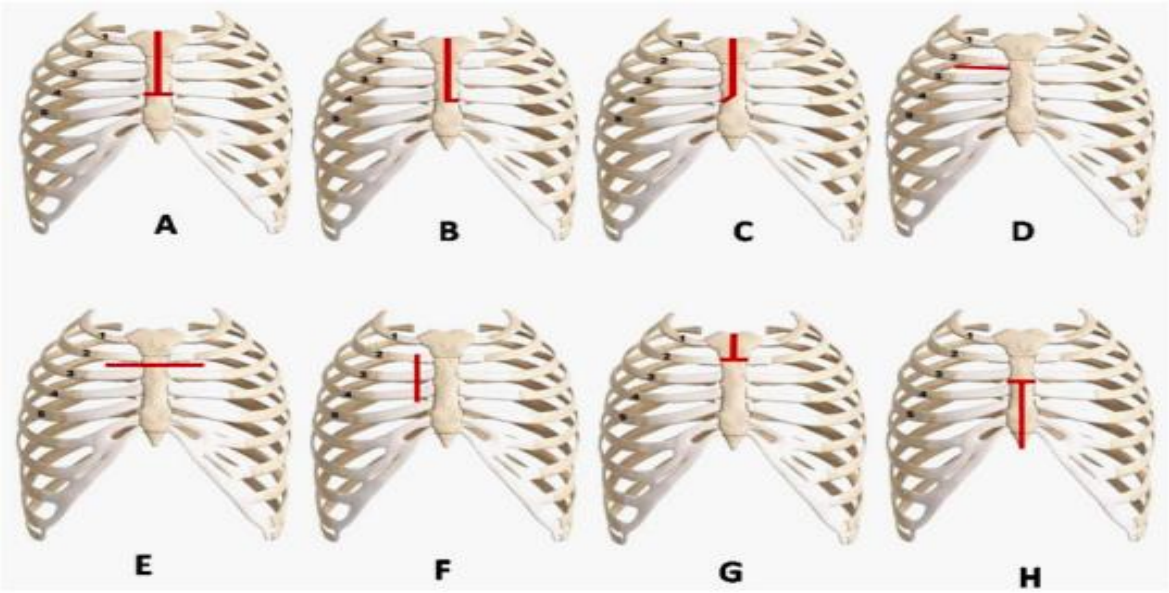

Figure 5. Incisions for minimally invasive aortic valve replacement. Inverted T partial sternotomy (A), L-hemisternotomy (B), J-hemisternotomy (C), right anterior thoracotomy (D), transverse sternotomy (E), right parasternal incision (F), manubrium-limited sternotomy (G), lower half sternotomy (H). Reproduced with permission from Nezafati MH, 2016. Under the Creative Commons Attribution 4.0 International License

The most commonly used approach is the J-hemisternotomy, which involves a small upper sternotomy up to the third intercostal space. It provides a familiar surgical window with direct and easy access to many cardiac structures, including the AV, ascending aorta, aortic root, pulmonary artery and the right atrium. In addition, conversion to a full sternotomy can be easily achieved in case of emergency.

During the past 23 years, minimally invasive AVR approaches have been increasingly used and recently became the standard procedure in many high-volume centers.

The early studies mini-invasive AVR has potential benefits, such as better patient satisfaction, less use of rehabilitation resources, early return to daily activities, less blood loss, early extubation, reduced wound infection and early discharge. An added benefit for the minimally invasive

approach was the ease of redo-surgery, as the pericardium remained intact with less adhesion formation.(20)

A review of the literature showed that numerous studies comparing short and long-term results of full sternotomy and minimally invasive techniques had been conducted for hemisternotomy AVR. Many argued that minimally invasive surgery's potential benefits might be offset by longer aortic cross-clamp and cardiopulmonary bypass times secondary to the limited surgical access and surgeon's learning curve.

A recent propensity-matched retrospective cohort by Aliahamd and his team has shown that ministernotomy AVR required longer clamp and cardiopulmonary bypass times without adversely affecting clinical outcome.(21) Shehada demonstrated in his retrospective study of 2103 patients who underwent primary isolated aortic valve replacement (MIAVR, n = 936); FSAVR, n = 1167), the aortic cross-clamp time (AXT) was not statistically different with low surgical mortality rate and excellent long-term survival.(22) Moreover, MIAVR was associated with shorter ventilation time, lower blood transfusion rate, a lower rate of postoperative respiratory and renal impairment.

The evolution of the rapid deployment or sutureless aortic prosthesis has also significantly altered implantation time. In a recent multicenter Canadian study from June 2011 to May 2013, 215 consecutive patients from 6 centers underwent sutureless AVR with the Perceval S (LivaNova PLC, London, UK) prosthesis via full, mini-sternotomy or mini-thoracotomy approaches.(23) Mazin and his colleagues demonstrated the use of the Perceval S prosthesis enhanced implantability in the setting of minimally invasive surgery with shorter operative time with excellent hemodynamic performance and clinical outcomes.(23)

Another factor that may influence the ischemic time is the operator learning curve. Nevertheless, surgeons' adoption of minimally invasive techniques, cross-clamp and cardiopulmonary times

have decreased dramatically over time. In a retrospective study by Soppa, 205 isolated, elective and urgent MIAVR cases performed by trainees demonstrated a low conversion rate with excellent safety.(24)

A few randomized controlled trials exist, but patient numbers are small and often incorporate more than one minimally invasive technique. Overall, prospective randomized trials and meta-analysis show advantages for MIAVR. Despite these advantages, there has been limited adoption of MSAVR by cardiac surgeons in Canada, particularly in British Columbia (BC). Until recently, St Paul's Hospital is the only medical center that offers the less invasive AVR approach for BC patients. Up to now, there is no study conducted to evaluate the effectiveness of ministernotomy over the standard approach in the management of aortic valve disease in BC.

At present, there are no guidelines to either recommend or discourage surgeons from using minimally invasive approaches to aortic valve surgery.(12, 13) The Society of Thoracic Surgeons Aortic Valve Guidelines for Management and Quality Measures refers to the potential and future benefits of minimally invasive surgery but makes no specific recommendations.(25) The International Society for Minimally Invasive Cardiothoracic Surgery (ISMICS) has no consensus guidelines on the subject of minimally invasive aortic valve replacement.(19) The main objectives of this research were to investigate the British Columbia experience with MSAVR and report contemporary results of MSAVR versus full sternotomy AVR (FSAVR) at St. Paul's Hospital.

Chapter 2: Study Methodology

2.1 Study Summary

Ministernotomy (MS) has been introduced recently as an alternative surgical technique for aortic valve replacements with potential advantages, including cosmetic benefit, reduction in postoperative pain, blood loss, hospitalization duration, and better wound healing addition to equivocal overall mortality rate. However, MIAVR is not widely adopted by the surgeons in British Columbia hospitals, and the clinical outcomes of MIAVR have not been formally studied. Considering the adverse effects of blood product transfusion, such as the risk of infection, transfusion-related acute lung injury (TRALI), hypersensitivity reaction and other adverse effects. One of the potential benefits of the minimally invasive approach is the decrease in blood loss and the need for blood product transfusion. Our research is the first in Canada to study the outcomes of MSAVR in BC patients and to show the benefits of MIAVR over the standard approach in decreasing the need for blood product transfusion and improvement in overall outcomes.

2.2 Study Design and Objectives

2.2.1 Study Design

A retrospective data review of patients with isolated aortic valve disease who underwent elective and non-emergent aortic valve replacement through a full or ministernotomy in the period from January 2007 to December 2016 at St. Paul's Hospital. Data was collected in an administrative database, the Cardiac Services BC (CSBC) registry.

Preoperative demographics, intraoperative events and postoperative outcomes have been collected as part of usual care. In this retrospective review, patients were stratified based on the

surgical techniques (full sternotomy vs ministernotomy). The need for blood transfusion was evaluated as well as the overall clinical outcomes in both cohorts. The study was approved by the St. Paul's Hospital and UBC Institutional Review Boards (CREB).

2.2.2 Hypotheses (Questions):

1. Does ministernotomy approach decrease the need for blood product transfusion in patient with aortic valve replacement in BC?
2. Does ministernotomy approach provide similar or better short and long-term survival in comparison to standard AVR in BC patients?
3. Does ministernotomy approach provide better clinical outcomes in comparison to standard AVR in BC patients?

2.2.3 Objectives:

1. To determine if there is any difference in the need for blood product transfusion between ministernotomy and full sternotomy aortic valve replacement in patients at St. Paul's Hospital up to seven days after surgery.
2. To determine if there is any difference in 30-day mortality between ministernotomy and full sternotomy AVR and other clinical outcomes.

2.3 Materials and methods

2.3.1 Inclusion Criteria

All patients aged 18 years or older who underwent isolated AVR through full and ministernotomy over the period from January 2007 to December 2016 at St. Paul's Hospital were included in this study.

2.3.2 Exclusion Criteria

- Patients who had any concomitant procedures involving the aortic root, ascending aorta and other valves, etc.
- Patients with previous open-heart surgery.
- Emergency cases.
- Patients with active endocarditis.

2.4 Endpoints

2.4.1 Primary outcome

- The incidence and the amount of intraoperative or postoperative blood product administration in the first 24 hours and up to 7 days following AVR.
- The need for re-exploration for bleeding.

2.4.2 Secondary outcomes

Secondary outcomes were a list of in-hospital morbidities, complications and covariates of interest. Standard STS definitions for postoperative events and complications were used.

2.4.2.1 Procedure related outcomes

- Cardiopulmonary bypass time.
- Aortic cross-clamp time.
- Type of prosthetic valve implanted.

2.4.2.2 Post-operative complications

- New-onset atrial fibrillation.
- Cerebrovascular accident.

- Renal dysfunction (increase in serum creatinine level > 2.0 or doubling of the most recent preoperative creatinine).
- Operative mortality was defined as all patient death occurred in the index hospital admission or within 30 days of surgery.

2.4.2.3 Length of stay

- Length of intensive care unit (ICU) stay.
- Total length of hospital stay.

2.5 Data collection

Patient demographic data such as age, sex, body mass index (BMI) was collected as baseline characteristic as well cardiac risk factors such as hypertension, diabetes, smoking and chronic steroid use. We categorized the data into three groups:

2.5.1 Preoperative

- New York Heart Association Class.
- Left Ventricular EF.
- The Canadian Cardiovascular Society grading of angina pectoris (CCS Class)

2.5.2 Intraoperative

- Surgical approach (full sternotomy or ministernotomy).
- Prosthetic type.
- Aortic cross-clamp and cardiopulmonary bypass time.
- The incidence and the amount of packed red blood cell (PRBC), plasma (PS) and platelet (PLT) transfusion.

2.5.2.1 Postoperative

- The incidence and amount of PRBC, PS and PLT transfusion.
- Reoperation for bleeding or tamponade.
- In hospital and 30-day mortality.
- Prolonged ventilation (>24 hours of mechanical ventilation).
- Post-operative hemorrhage or tamponade.
- New onset of atrial arrhythmia.
- Cerebrovascular accident.
- New hemodialysis.
- Sternum wound infection.

2.6 Operative technique

St. Paul's Hospital center introduced J-hemisterntomy MSAVR in 2003 by a single surgeon (Dr. Anson Cheung) and adopted it in his practice as a standard approach for all isolated AVR. The remaining surgeons performed aortic valve replacements via a conventional full sternotomy. For MSAVR, a 5 cm skin incision was made below the sternal notch to the third intercostal space. A J-hemisternotomy is created by dividing the sternum longitudinally and transversely to the right into the third intercostal space. This procedure is depicted in Figures 6 and 7. CPB was established via aortic cannulation with a 20 or 22F DLP wire reinforced aortic cannula (Medtronic, Minneapolis, USA) at the level of the distal ascending aorta. Central venous drainage with right atrial cannulation using a 29F 3-stage venous cannula (Medtronic, Minneapolis, USA). Vacuum-assisted was used in some cases to promote venous drainage as necessary. Myocardial protection was achieved by antegrade and retrograde cardioplegia using blood micro-cardioplegia. LV

venting was achieved via the right superior pulmonary vein or pulmonary artery cannulation. A transverse aortotomy was performed, followed by standard aortic valve implantation using interrupted, pledgetted and hand-tied braided sutures supra-annularly.

The aortotomy was closed in two layers in the standard fashion. One pericardial drain and ventricular pacing wires were placed in all patients. Atrial wires were placed if indicated.

Ministernotomy closure was performed with two stainless steel wires in the manubrium and another two wires in the body of the sternum. For the conventional technique, a standard median sternotomy was performed. CPB was via the ascending aorta and two-stage right atrial cannulation for venous drainage. The technique for venting was at the surgeon's discretion. Antegrade and/or retrograde blood micro-cardioplegia was used for myocardial protection. All valves were inserted using either interrupted or continuous suture technique. A double-layer technique was used for aortotomy closure.

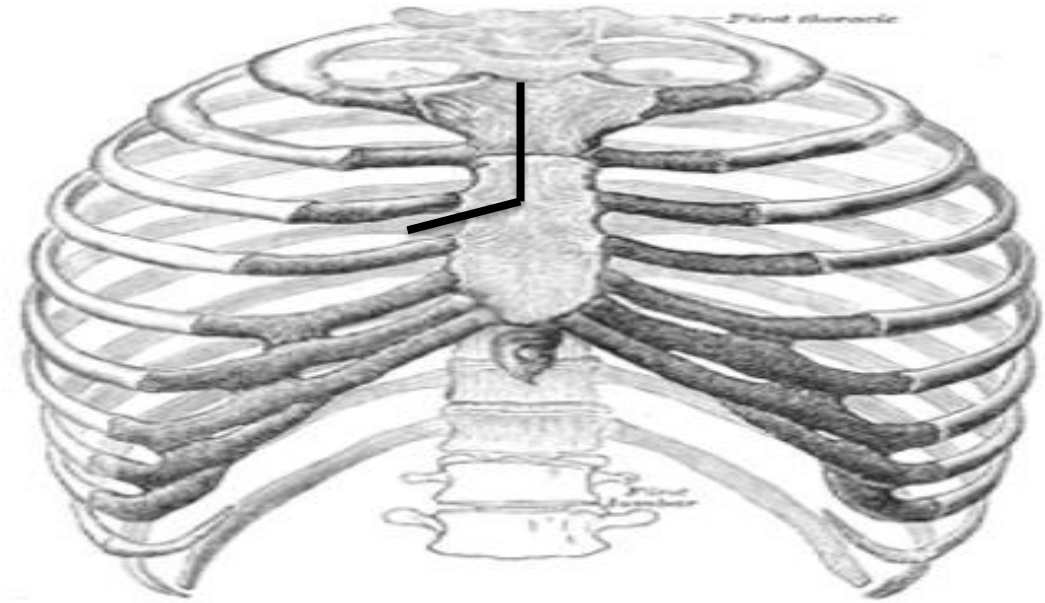

Figure 6. A J-hemisternotomy, the surgical technique used in this cohort at St. Paul's Hospital. The sternum was divided longitudinally and a transversely into right third intercostal space. (Source: ***Gray's Anatomy of the Human Body***, 20th ed. 1918)

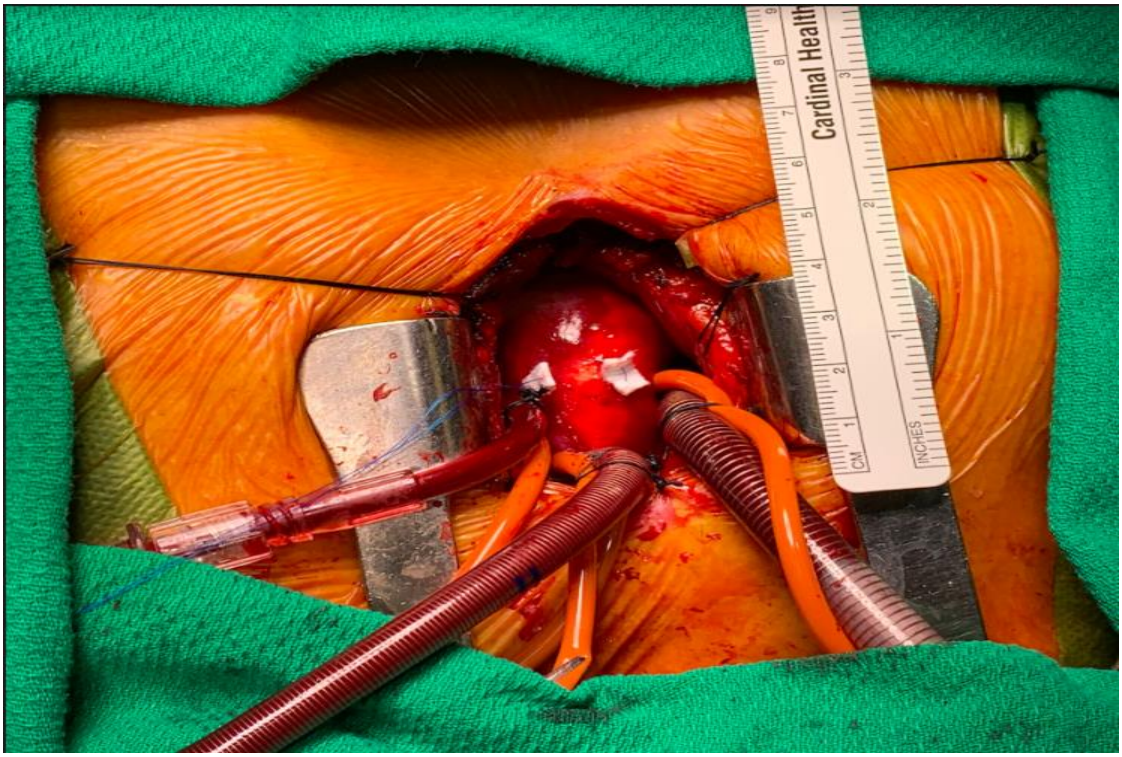

Figure 7. A 5 cm J-hemisternotomy with central aortic, venous cannulation and pulmonary venting. (Courtesy of Dr. Anson Cheung)

2.7 Statistical plans

2.7.1 Data source

After obtaining Research Ethics Approval, the Cardiac Services BC (CSBC) registry was contacted to obtain the desired data extracted from the archived medical charts and electronic medical records. We categorized the data into three groups: 1- preoperative, 2- intraoperative and 3- postoperative. There were some limitations to the CSBC database. Blood product usage was

only available for surgery performed from 2007 to 2016, and deposition time was available from 2010 only. Missing data were obtained by performing a chart review.

2.7.2 Data analyses

Patient demographics and operative data are summarized as mean ± standard deviation, median with 25th to 75th percentiles or prevalence, as appropriate. The MSAVR and FSAVR groups were compared using the Chi-squared test for categorical variables and *t*-test or Wilcoxon rank-sum test, as appropriate for continuous variables.

To reduce the effect of selection bias and potential confounding hazards in this observational study, we performed an inverse probability of treatment weighting (IPTW) analysis using the propensity score. The propensity score indicated the predicted probability of receiving MSAVR treatment, calculated using a non-parsimonious multiple logistic regression analysis from the logistic equation for each patient. There were few significant differences in baseline characteristics between groups on univariate analysis. Therefore, there was a limited role for more sophisticated matching techniques, given how similar the groups were at baseline, and given that we hoped to retain as much power as possible. The primary results presented are, therefore, comparisons of the unmatched groups. We did perform a sensitivity analysis using IPTW and confirmed that the propensity analysis gave similar results as the primary unmatched analysis. The results of this IPTW analysis can be found in the Appendix.

The univariate and multiple logistic regression model was conducted to explore the risk factors for blood product transfusion. Simultaneously, the association between post-procedure hospital length of stay (LOS) and surgery type was assessed using a negative binomial regression model adjusted with other risk factors. Kaplan-Meier method was used to examine patient survival.

Patients were censored at the time of their last follow-up visit or at the time of death if the outcome of the interest had not occurred. Categorical predictors of the outcome were individually tested for equality of survival with a log-rank test. In order to account for confounders, proportional hazard regression models were developed. The proportional hazard assumption of Cox regression was tested based on the Schoenfeld residuals. All of the model selections were developed by incorporating all variables using multivariate model selection procedures (both stepwise selection and backward elimination techniques) with statistical significance of inclusion and exclusion at $p<0.05$. All reported p values are 2-tailed under the conventional 5% level of significance, and all statistical analysis was performed with SAS software version 9.4 (SAS Institute, Cary, North Carolina).

Chapter 3: Results and Discussion

3.1 Results

3.1.1 Baseline characteristics

Between January 2007 to December 2016, 910 patients underwent isolated aortic valve replacement at St. Paul's Hospital, of which 776 underwent FSAVR and 134 had MSAVR. Patient's demographic data are shown in Table 3. The mean age in years for both groups was comparable (Mean 70.7 ± 11.8 in MSAVR vs 69.7 ± 12.2 in the FSAVR group, p=0.38), and more than 40% of patients in both surgery groups were female. The overall median follow-up time was 6.2 years (95% CI 3.8 - 8.5) for the entire cohort, 5.2 years (95% CI 2.8 - 7.6) for FSAVR, and 6.5 (95% CI 4.1 - 8.6) years for MSAVR patients. Multivariable analysis was used to compare the two surgical groups adjusting for baseline characteristics.

There was no significant difference in the selected baseline variables between the two surgical groups, except for LV ejection fraction (LVEF), New York Heart Association (NYHA) and Canadian Cardiovascular Society grading of angina pectoris (CCS). MSAVR group had a higher proportion of patients in NYHA class III/IV (77.5% vs 49.3%, p<0.001) and had a higher incidence of pre-existing renal failure (12.7% vs 8.8%), though not statistically significant (p=0.15).

Table 3. Baseline characteristics of isolated AVR patients

Variable	All (n=910)	FSAVR (n=776)	MSAVR (n=134)	*p* value
Age (year)	69.8 ± 12.1	69.7 ± 12.2	70.7 ± 11.8	0.38
BMI (kg/m2)	28.6 ± 5.9	28.6 ± 5.9	28.8 ± 6.0	0.69
Body surface area (m^2)	1.9 (1.8, 2.1)	1.9 (1.8, 2.1)	2.0 (1.8, 2.1)	0.64
Preop hemoglobin (g/L)	133.9 ± 17.8	133.7 ± 18.1	134.8 ± 16.6	0.53
Preop platelet count	199 (165, 244)	198 (164, 241)	210 (168, 267)	0.09
Female	383 (42.1)	323 (41.6)	60 (44.8)	0.50
LV ejection fraction <50%	248 (27.3)	226 (29.1)	22 (16.4)	0.002
NYHA class III/IV	485 (53.3)	382 (49.3)	103 (77.5)	<0.001
CCS class				0.020
1	61 (6.7)	47 (6.1)	14 (10.4)	
2	174 (19.2)	159 (20.6)	15(11.2)	
3	99 (10.9)	83 (10.7)	16 (11.9)	
4	25 (2.8)	24 (3.1)	1 (0.7)	
Hypertension	671 (74.1)	563 (72.9)	108 (80.6)	0.06
Diabetes	217 (23.8)	181 (23.3)	36 (26.9)	0.37
Current smoker	67 (7.4)	55 (7.1)	12 (9)	0.44
Prior MI	86 (9.5)	72 (9.3)	14 (10.4)	0.67
Chronic steroid use	15 (1.7)	12 (1.6)	3 (2.2)	0.57
Liver disease	110 (12.1)	97 (12.6)	13 (9.7)	0.35
Renal dysfunction (eGFR <60 and >15)	159 (17.6)	138 (17.9)	21 (16)	0.60
Renal failure (eGFR<15)	85 (9.3)	68 (8.8)	17 (12.7)	0.15
Dialysis	19 (2.1)	15 (1.9)	4 (3)	0.43
COPD	199 (21.9)	173 (22.3)	26 (19.4)	0.46
Pulmonary hypertension	149 (16.4)	123 (15.9)	26 (19.4)	0.32
Coagulopathy (hyper and hypo)	13 (1.4)	11 (1.4)	2 (1.5)	0.95

Values are shown as mean ± SD, or median (Q1, Q3), or n (%). CCS: Canadian Cardiovascular Society grading of angina pectoris; NYHA: New York Heart Association.; MI: myocardial infarction; COPD: chronic obstructive pulmonary disease. Q1, Q3: first and third quartile. Percentages calculated with complete observations. P values were obtained using a *t*-test or Wilcoxon rank test for continuous variables, Chi-squared test for categorical variables.

3.1.2 Primary outcomes

3.1.2.1 Freedom from blood transfusion and reoperation for bleeding

Table 4 shows the need for blood product transfusion between the two surgical approaches. The incidence of blood product transfusion was statistically significant between the two groups. The freedom from blood product transfusion in the MSAVR group was significantly higher than the standard approach **(**65.7% vs 49.6 % respectively, $p<0.001$, $\alpha=5\%$). Once a patient required any blood product transfusion, the average number of units transfused was 5, with a median of 3 in both groups ($p = 0.97$). The risk of reoperation for bleeding was lower in the MSAVR group, 1.5 % vs 2.6 %; however, it was not statistically significant. (Table 4)

Table 4. Summary of blood product transfusion (PRBC/plasma/platelets) by surgical type

Variables	All (n=910)	FSAVR (n=776)	MSAVR (n=134)	*p* value
Blood product transfusion				<0.001†
No	472 (52.0)	384 (49.6)	88 (65.7)	
Yes	436 (48.0)	390 (50.4)	46 (34.3)	
Unit of numbers transfused (Mean ± SD)	5.3 ± 6.6	5.3 ± 6.7	5.0 ± 5.1	0.97‡
Unit of numbers transfused (Median (q1, q3)	3 (2, 6)	3 (2, 6)	3 (2, 7)	
Reoperation for bleeding	22 (2.4)	20 (2.6)	2 (1.5)	0.45†

Two patients in FSAVR group had missing information on blood product transfusion. Values shown as n (%) if not specified. Calculation based on complete data. † Chi-Square test was conducted. ‡ Mean or median calculated based on the sum of blood product counts for the 436 patients receiving blood transfusion. Wilcoxon rank sum test was conducted.

3.1.2.2 The intraoperative and postoperative blood products administration in the first 24 hours and up to 7 day following AVR

Table 5 summarizes the amount of blood product administrated in the first 24 hours and the first seven-day post-surgery. With regards to the type of blood product, plasma (PS) was the most commonly used in both groups within the first day and a week post-surgery. The need for plasma

was statistically significantly lower in the MSAVR group. (20% vs 30.1%, p=0.017) in the first 24 hours and in the first 7-day post-surgery (21.4% vs 33 %, p=0.007). The need for platelets (PLT) transfusion was not a statistically significant difference in the first 24 hours (MSAVR 6.9% vs FSAVR 12.0%, p=0.09); however, it was significantly lower at seven days in the MSAVR cohort (6.9% vs 13.7 %, p=0.032)

The transfusion rate for PRBC was 15% for the entire study cohort in the first 24 hours and 20.8 % in the first week. The PRBC transfusion rate was observed to be insignificantly higher in the full sternotomy population (15.5% vs 12.4 %, p=0.41) in the first 24 hours and the first week (21.4% vs 16.6 %, p=0.22). No massive blood transfusion (PRBC >10 units) occurred in the MSAVR (0.0% vs 0.7, p=0.99) in the first 24 hours and during the first 7 days (0% vs 4.1%, P=0.60).

Table 5. Summary of MNEMONIC type by surgical type for entire 910 patient cohort

First 24 hours	All n=910	FSAVR n=776	MSAVR n=134	*p* value
Received PS	301 (28.7)	272 (30.1)	29 (20.0)	0.017
Not received PS	749 (71.3)	633 (69.9)	116 (80.0)	
Received PLT	119 (11.3)	109 (12.0)	10 (6.9)	0.09
Not received PLT	931 (88.7)	796 (88.0)	135 (93.1)	
Not received RBC	892 (85.0)	765 (84.5)	127 (87.6)	0.41
Received RBC	158 (15.0)	140 (15.5)	18 (12.4)	
RBC more than 4†	26 (16.5)	22 (15.7)	4 (22.2)	0.50
RBC more than 10†	1 (0.6)	1 (0.7)	0 (0.0)	0.99
First 7 days	**All n=910**	**FSAVR n=776**	**MIAVR n=134**	***p* value**
Received PS	330 (31.4)	299 (33.0)	31 (21.4)	0.007
Not received PS	720 (68.6)	606 (67.0)	114 (78.6)	
Received PLT	134 (12.8)	124 (13.7)	10 (6.9)	0.032
Not received PLT	916 (87.2)	781 (86.3)	135 (93.1)	
Not received RBC	832 (79.2)	711 (78.6)	121 (83.4)	0.22
Received RBC	218 (20.8)	194 (21.4)	24 (16.6)	
RBC more than 4†	51 (23.4)	46 (23.7)	5 (20.8)	0.99
RBC more than 10†	8 (3.7)	8 (4.1)	0 (0.0)	0.60

Values shown as n (%). P values were obtained from Chi-square test between two surgical groups. †Calculation based on "Received RBC". 436 of 910 patients received blood transfusion, 390 with FSAVR, 46 with MIAVR, receiving at least one of MNEMONIC types (PS, PLT or RBC), in total, 436 patients received 578 types, 521 in FSAVR and 57 in MIAVR. 472 patients did not receive blood transfusion, 384 with FSAVR, 88 with MIAVR. The percentages in the column "All" were calculated based on 1050=578+472, in "FSAVR" based on 905=521+384 and in "MIAVR" based on 145=57+88.

3.1.2.3 Predictors of blood product transfusion following AVR

Table 6 shows the logistic regression model for predictors for blood product transfusion following AVR. 436 out of 910 patients received blood product transfusion, and two patients had

missing blood product transfusion information. In the univariate analysis of variables and their statistical significance, 12 variables were found to have a potential association with the risk of receiving blood product transfusion. Incision type (OR 1.93, 95% CI 1.32 - 2.84, p<0.001), age (OR 1.02, 95% CI 1.01 - 1.03, p<0.001), low BMI (OR 0.95, 95% CI 0.93 - 0.97, p<0.001), low LVEF, presence of liver disease, presence of CHF and longer pump time were significant independent predictors for blood product transfusion.

Multivariate analysis revealed eight significant variables for blood product transfusion including incision type (OR 2.23, 95% CI 1.44 - 3.45, p < 0.001), age (OR 1.02, 95% CI 1.01 - 1.04, p =< 0.001), BMI (OR 0.77, 95% CI 0.65 - 0.91, p=0.003), LVEF <50 (OR 1.83, 95%CI 1.31 - 2.56, p=<0.001), CHF (OR 1.95, 95% CI 1.43 - 2.66, p=<0.001), pump time per 30 min (OR 1.63, 95% CI 1.38 -1.93, p<0.001). Not surprisingly, higher BMI (linear term) is slightly protective. The multivariate Cox regression model showed several independent predicted factors for the blood product transfusion. In the multivariant analysis, full sternotomy, age, low ejection fraction, CHF, and longer pump time were significant predictors for blood product transfusion in both surgical groups. Patients with FSAVR had a 22% likelihood of receiving any blood product transfusion. Patients in the less invasive group were less likely to receive blood products and received fewer units (OR 2.23, 95% CI 1.44 - 3.45, p=0.001)**.** Patients with higher BMI had a lower likelihood of receiving blood product transfusion with OR 0.77, 95% CI 0.65 - 0.91, p= 0.003. Patients with longer pump time were at increased odds of receiving blood product transfusion (OR 1.63, 95% CI 1.38 - 1.93, p=<0.001)

Table 6. Logistic regression analysis on blood product transfusion

Parameter	Univariate analysis		Multivariate analysis	
	Odds Ratio (95% CI)	***p* value**	**Odds Ratio (95% CI)**	***p* value**
Full Sternotomy	1.93 (1.32 - 2.84)	<0.001	2.23 (1.44 - 3.45)	<0.001
Age (years)	1.02 (1.01 - 1.03)	<0.001	1.02 (1.01 - 1.04)	<0.001
Female	1.19 (0.93 - 1.55)	0.20		
BMI (kg/m^2)	0.95 (0.93 - 0.97)	<0.001	0.77 (0.65 - 0.91)	0.003
BMI^2	--	--	1.00 (1.00, 1.01)	0.014
LV ejection fraction <50%	1.56 (1.16 - 2.09)	0.003	1.83 (1.31- 2.56)	<0.001
Prior MI	1.65 (1.05 - 2.59)	0.030		
Liver disease	2.46 (1.61 - 3.75)	<0.001	1.722 (1.088 – 2.727)	0.020
Renal dysfunction	1.54 (1.09 - 2.18)	0.014		
Dialysis	3.83 (1.29 - 11.33)	0.015	3.460 (1.097 – 10.91)	0.034
COPD	1.49 (1.09 - 2.04)	0.014		
Pulmonary hypertension	1.40 (0.98 - 1.99)	0.06		
CHF	1.84 (1.41 - 2.39)	<0.001	1.95 (1.43 - 2.66)	<0.001
Pump time (per 30 min)	1.51 (1.30 - 1.76)	<0.001	1.63 (1.38 - 1.93)	<0.001

The multiple logistic regression model was generated using backwards selection algorithm with statistical significance of inclusion and exclusion at p<0.05 and variables selected using clinical judgement. Firth's penalized likelihood approach was used. P value =0.60 from Hosmer and Lemeshow Goodness-of-fit test showed that the model selected is suitable and final C statistic is 0.72. MI: myocardial infarction; COPD: chronic obstructive pulmonary disease. CHF: congenital heart failure; CI = confidence interval. BMI2=BMI*BMI

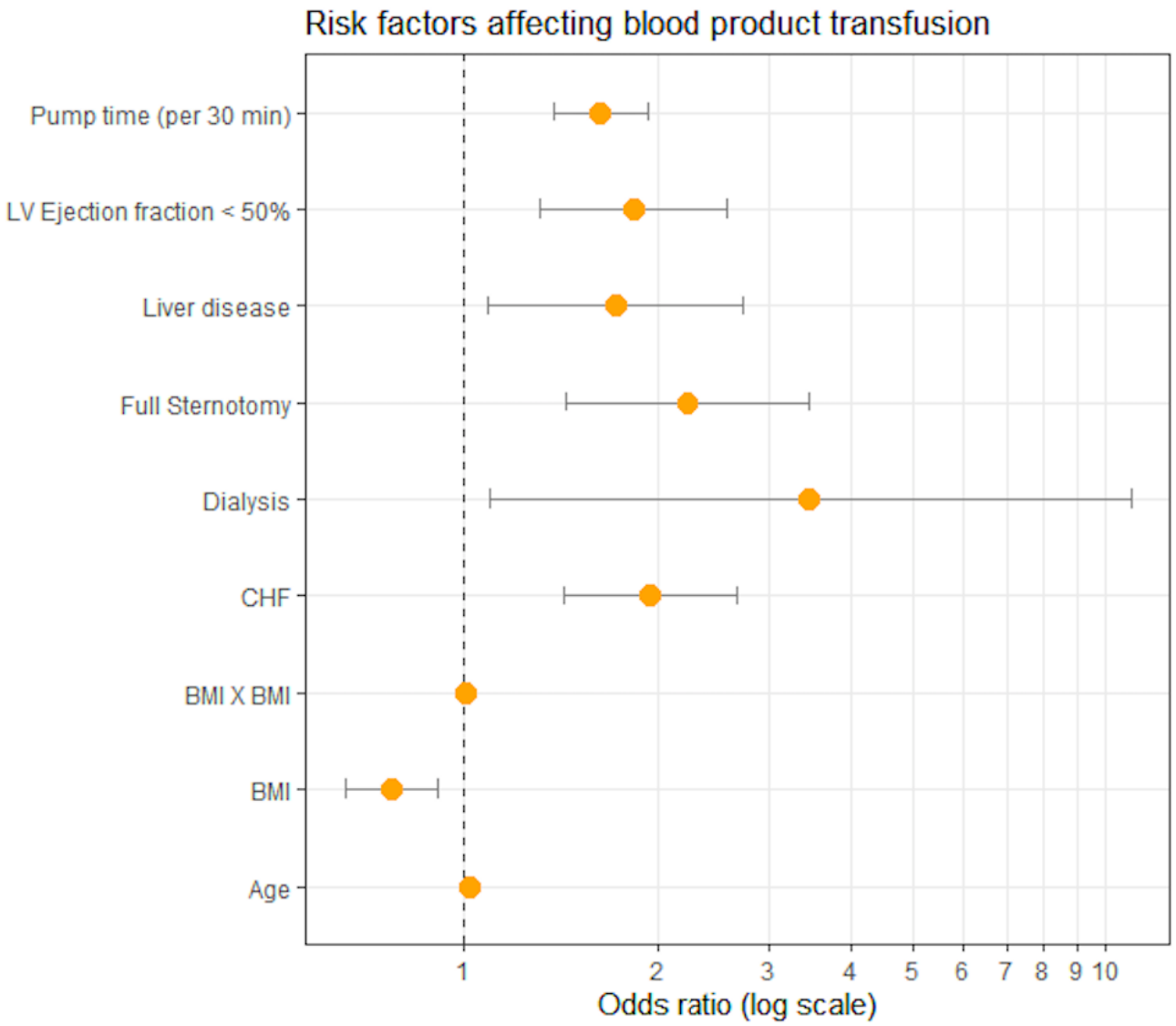

Figure 8. Forest plot of odds ratio from multivariate logistic regression analysis

3.1.3 Secondary Outcomes

3.1.3.1 Procedure related and post-operative complications

Clinical outcomes are summarized in Table 7. Biological tissue prostheses were implanted more frequently and not different in both groups (MSAVR 93.3% and FSAVR 93.8%, p=0.84). The CBP and AXT times were approximately 9 and 6 minutes shorter in the MSAVR group than FSAVR, respectively (mean CBP 75.4 ± 14.7 vs 84.3 ± 30.0, p=0.014, and mean AXT 58.5 ± 12.2 vs 64.7 ± 24.7, p=0.08, respectively). The overall mean length of hospital stay was one day shorter in the MSAVR group (7.8 vs 8.6 days, p=0.006).

There were no significant differences in the incidence of new-onset atrial arrhythmias, including atrial fibrillation (MSAVR: 43%, FSAVR: 45%, p=0.69) or the incidence of CVA (MSAVR: 1.9%, FSAVR: 1.3%, p=0.64). Despite the higher incidence of preoperative renal disease in the MSAVR group, there was no significant difference in the incidence of new hemodialysis between the two groups (MSAVR: 2.8%, FSAVR: 2.4%, p=0.82).

No significant differences were found between groups with respect to the incidence of prolonged ventilation and postoperative hemorrhage or tamponade. There was no sternal wound infection in the MSAVR group where the incidence in the FSAVR was low at 1.1% and not statistically significant.

Table 7. Clinical outcomes of patients underwent ministernotomy and full sternotomy aortic valve replacement at St. Paul's Hospital

Clinical outcomes	FSAVR (n=776)	MSAVR (n=134)	*p* value
Pump time (min)	84.3 ± 30.0	75.4 ± 14.7	0.014
Clamp time (min)	64.7 ± 24.7	58.5 ± 12.2	0.08
Discharge hemoglobin (g/L)	106.6 ± 13.7	108.1 ± 13.4	0.26
Discharge platelet count	192 (153, 259)	180 (140, 238)	0.16
Prosthesis type			0.84
Bioprosthetic	556 (93.8)	111 (93.3)	
Mechanical	37 (6.2)	8 (6.7)	
Length of stay in hospital (days)	8.6 ± 7.2	7.8 ± 6.3	0.006
New onset of atrial arrhythmia	277 (45)	46 (43)	0.69
Sternum wound infection	7 (1.1)	0 (0.0)	0.27
Postoperative hemorrhage/tamponade	12 (2.0)	2 (1.9)	0.96
CVA	8 (1.3)	2 (1.9)	0.64
New hemodialysis	15 (2.4)	3 (2.8)	0.82
Prolonged ventilation	63 (10.2)	9 (8.4)	0.56

Values are shown as mean±sd, or median (Q1, Q3), or n (%). Q1, Q3: first and third quartile. Percentages calculated with complete observations. P values are obtained using a t-test or Wilcoxon rank test for continuous variables, Chi square test for categorical variables. No cases found for valvular non-structural dysfunction and valvular thrombosis. Values shown as n (%) and calculated on complete observations. P values obtained using Chi sq-test. * Values calculated based on the BC patients**.**

3.1.3.2 The 30-day mortality and long-term survival

The overall 30-day mortality for the entire cohort was 0.5% (5/910), 0.5% (4/776) in the full sternotomy and 0.7% (1/134) in the ministernotomy group, respectively. There was no significant difference in the 30-day mortality between the two surgery groups (p=0.79). The overall median follow-up time was 6.2 [3.8, 8.5] years, 5.2 [2.8, 7.6] years for the patients with full sternotomy surgery, and 6.5 [4.1, 8.6] years for the patients with ministernotomy. The entire cohort's overall long-term survival was 75.6%; 688 were alive at a median follow-up of 6.2 years. Figure 9 illustrates the Kaplan-Meier curve of long-term survival following MSAVR and FSAVR groups.

No significant difference was observed in the long-term survival between groups in both Kaplan-Meier analysis (log-rank test p=0.70) and univariate Cox proportional hazards regression model (Hazard ratio 0.92, 95% CI 0.61 - 1.40, p=0.70). In the Kaplan-Meier analysis, the long-term survival of FSAVR and MSAVR follows an almost identical pattern. Each group had a survival rate higher than 80% at 4 years, and at least 70% survived up to 6 years. At 10 years, the survival rate of each group is higher than 50%. Since the cumulative incidence curve does not get to 50% or above, therefore the median survival time cannot be computed from this data (Figure 9).

The multivariate Cox regression model showed that age, sex, BMI, preoperative Hgb, liver disease, renal failure, COPD and presence of pulmonary hypertension were independent risk factors affecting long-term survival. For each one-year increase in age, survival was reduced significantly (Hazards ratio 1.05, 95% CI 0.034 - 1.068, p<0.001). A significantly higher survival was observed in the female patients than the male patients (Hazard ratio 0.72, 95% CI 0.54 - 0.96, p=0.024). Patients with pulmonary hypertension had worse long-term survival (Hazards ratio 1.79, 95% CI 1.33 - 2.41, p<0.001) and similarly for those with pre-existing poor renal function had a worse prognosis (Hazards ratio 1.74, 95% CI 1.05- 1.88, p=0.007) (Table 8).

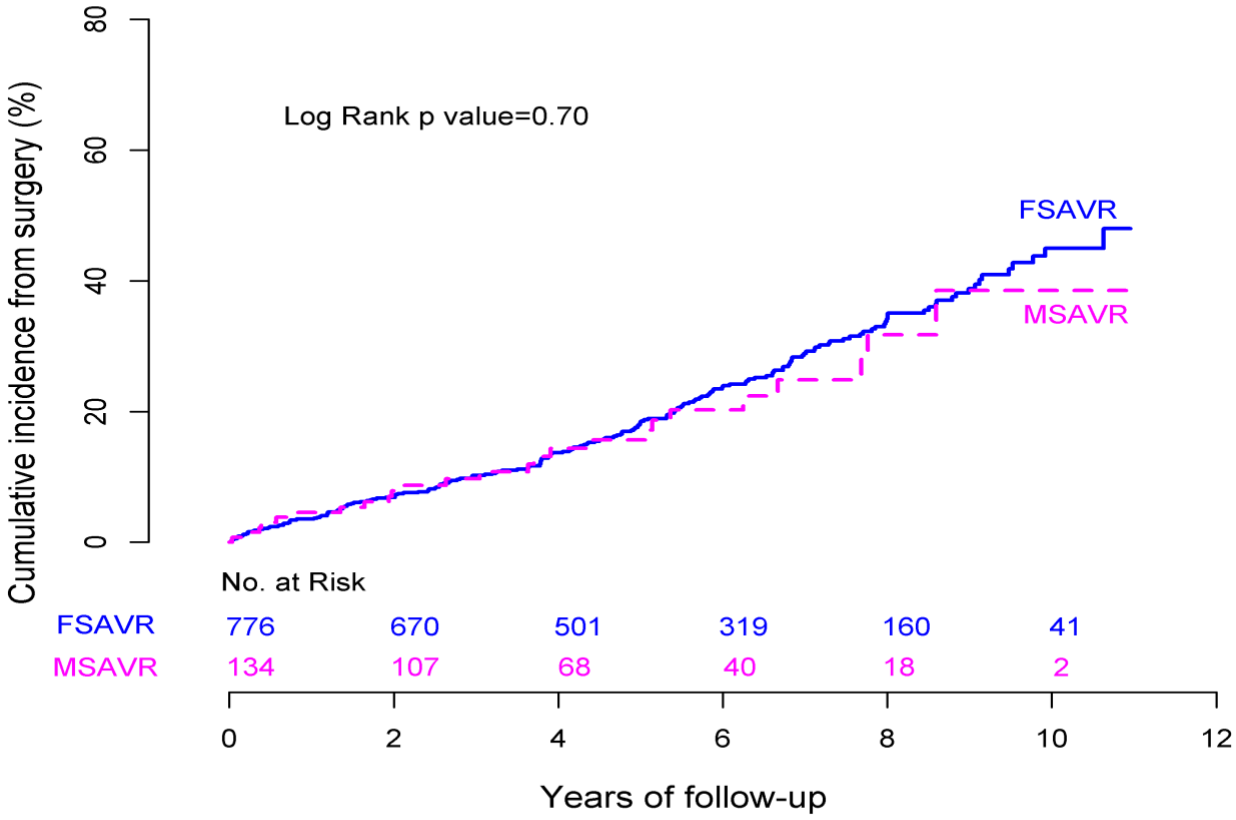

Figure 9. Kaplan-Meier curve of long-term survival following FSAVR and MSAVR (before IPTW)

Table 8. Cox PH multivariate regression analysis for long term survival in patients

Parameter	Univariate model		Multivariate model	
	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Full Sternotomy	0.921 (0.607, 1.398)	0.70	1.005 (0.656, 1.540)	0.98
Age (year)	1.058 (1.043, 1.074)	<0.001	1.051 (1.034, 1.068)	<0.001
Female	1.176 (0.904, 1.531)	0.23	0.717 (0.538, 0.957)	0.024
BMI	0.998 (0.975, 1.022)	0.87	0.813 (0.724, 0.914)	<0.001
BMI^2	--	--	1.003 (1.002, 1.005)	<0.001
Preop hemoglobin (g/L)	0.972 (0.966, 0.979)	<0.001	0.980 (0.972, 0.987)	<0.001
Liver disease	1.692 (1.216, 2.354)	0.002	1.500 (1.061, 2.119)	0.022
Renal failure	2.862 (1.978, 4.140)	<0.001	1.742 (1.168, 2.598)	0.007
COPD	1.972 (1.493, 2.606)	<0.001	1.407 (1.051, 1.883)	0.022
Pulmonary hypertension	2.205 (1.646, 2.954)	<0.001	1.788 (1.325, 2.412)	<0.001
NYHA (III+IV)	1.680 (1.277, 2.210)	<0.001		
LV ejection fraction <50%	1.079 (0.813, 1.432)	0.60		
Hypertension	1.576 (1.122, 2.213)	0.009		

COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association. BMI^2=BMI*BMI

3.1.4 Length of hospital stay

In general, the MSAVR group had a significantly shorter LOS in the hospital with a mean of 7.8 ± 6.2, while the FSAVR patient stayed one day longer at 8.6 ± 7.2 (p=0.006). When adjusted with baseline covariates in a negative binomial regression model, the expected LOS for the MSAVR group was 8.8% shorter than the FSAVR group. However, the difference was not statistically significant (p=0.11). For each one-year increase in age, the expected log count of LOS increased by 0.009 (p<0.001). Females tended to stay shorter in the hospital (the expected log count of LOS -0.071, 95% CI -0.15-0.01, p=0.09). It was not surprising that patients with coexistent comorbidity stayed longer in the hospital (Table 9).

Table 9. Regression model for predictors for longer hospital length of stay following AVR

Parameter	Estimate	Standard Error	Wald 95% Confidence Limits		*p* value
Incision type (mini)	-0.092	0.057	-0.203	0.0197	0.11
Age (year)	0.009	0.0017	0.006	0.012	<0.001
female	-0.071	0.0416	-0.153	0.010	0.09
Preop hemoglobin (g/L)	-0.005	0.0012	-0.007	-0.003	<0.001
LV ejection fraction (<50%)	0.101	0.044	0.016	0.186	0.021
NYHA (III/IV)	0.092	0.042	0.010	0.174	0.028
CCS*					
Class 1	-0.019	0.078	-0.171	0.133	0.81
Class 2	-0.056	0.052	-0.158	0.046	0.28
Class 3	0	0.063	-0.124	0.124	0.99
Class 4	0.468	0.108	0.256	0.679	<0.001
Liver disease	0.146	0.058	0.033	0.260	0.012
Renal dysfunction	0.167	0.072	0.027	0.308	0.019
Dialysis	0.282	0.142	0.005	0.559	0.046
COPD	0.114	0.046	0.023	0.204	0.014
Pulmonary hypertension	0.121	0.051	0.021	0.222	0.018

Comments: Since the mean is far different from its variance, a negative binomial distribution is assumed for the length of stay in hospital. Backwards selection method used with probability 0.10 using all the variables listed in Table 3. * Reference: CCS='None'. COPD: chronic obstructive pulmonary disease.

3.2 Discussion

Surgical aortic valve replacement is the gold standard in the management of severe symptomatic aortic valve stenosis. It is a safe and well-established procedure with an overall hospital mortality rate of less than 2%. (14)However, as the population ages, the number of elderly AS patients with significant comorbidity poses an increased surgical risk. Therefore, many elderly patients were not referred to or denied surgical correction. The less invasive surgical approach may be beneficial in the elderly and high-risk cohort. Many less invasive approaches have been described, and the mini-sternotomy AVR at St. Paul's Hospital was our study focus. Much uncertainty still exists about whether the less invasive approaches, particularly the mini-sternotomy approach, provide equivalent or superior results comparing to the standard practice. Some studies have shown the

beneficial effects of minimally invasive techniques in replacing the aortic valve, but others have shown that the traditional approach still provides excellent clinical outcomes. It is worth mentioning that studies that had unfavourable outcomes of less invasive procedures were in the infancy of those techniques with limited experience and various surgical approaches.

Adaptation of new and less invasive technique was slow initially. Taking into account that a smaller incision with added technical challenges necessitating a steep learning curve for the surgeon and surgical team. Many prospective randomized studies and meta-analyses have shown some benefits of a less invasive approach in comparison to the more invasive standard approach.

Less postoperative pain, bleeding, shorter recovery time, lower incidence of the chest and sternal wound infections, lower incidence of arrhythmias, shorter hospital stay, better cosmesis and lower cost. (26)Despite these benefits, only 10% of isolated AVR were being performed minimally invasively in the US.(27-29) The phenomena were not different in British Columbia, where there is slow uptake of this technique and the clinical outcome of mini-sternotomy AVR have not been reported. My project was the first to evaluate this approach's safety and effectiveness by evaluating the need for blood product transfusion and other clinical outcomes in BC patients.

3.2.1 Primary outcomes

3.2.1.1 Need for blood product transfusion, the amount of blood product administration in the first 24 hours and up to 7 days following AVR and the risk of reoperation for bleeding

The administration of allogeneic blood product transfusion is common in cardiac surgery. Although it is necessary to transfuse in patients with anemia and bleeding, administration of blood products is associated with suppressing the immune system triggering adverse reactions, thus contributing to patient morbidity post-surgery.

A large number of published studies described the link between transfusion and worsening of short and long-term outcomes following cardiac surgery. (30, 31) Blood transfusion is associated with transfusion-related acute lung injury, decreased quality of life, decreased short and long-term survival, and increased resource utilization and cost. Additionally, there is a small risk of viral transmission from a blood donor. (32) Consequently, blood loss and the subsequent blood transfusion requirement (PRBC) and other blood products are critical indicators for quality assurance. More than one-third of the patient undergoing full sternotomy AVR develop clinically significant bleeding and require postoperative PRBC transfusion. (30, 33) As MIAVR minimizes mediastinal dissection and mediastinal bleeding, a lower requirement for blood product transfusion and re-exploration for bleeding are expected. Our study found that the transfusion requirement of blood products was significantly reduced in the MSAVR group. Freedom from blood product transfusion increased dramatically from 49.6% in the control group to 65.7% in the MSAVR group. No patient in the MSAVR group required massive transfusion (more than ten units of PRBC) in the first 24 hours or up to seven days post-surgery. Reoperation for bleeding or tamponade was lower in the MSAVR group; though it was clinically significant, it did not achieve statistical significance due to the small sample size. Similar results were found in prior studies; mini-AVR is associated with decreased blood product utilization. (34-37)

3.2.2 Secondary outcomes

3.2.2.1 Procedure-related

3.2.2.1.1 Cardiopulmonary bypass and aortic cross-clamp times

Due to the technical challenges with limited surgical window with less invasive approaches and a steeper surgeon's learning curve, many early studies showed prolongation in cardiopulmonary and aortic cross-clamp time. The more extended CBP and AXT may be associated with adverse

outcomes, including myocardial ischemia, risk of atrial fibrillation and acute kidney injury. (38)However, many recent studies did not identify any negative clinically significant effects with prolongation in CBP and AXT time. In a recent prospective randomized study with one hundred patients randomized into ministernotomy and full sternotomy AVR by Petar Vukovic and his colleagues, despite significantly longer CBP and XC time in the mini-sternotomy group, no clinically or statistically significant outcomes were found. (39)Additional studies by Aliahmed, Glauber had similar results. (21, 40)

Contrary to other studies, we reported a significant reduction in CPB and XC time in the less invasive AVR group. A possible explanation for this finding may be MSAVR was performed by a single surgeon with prior experience in minimally invasive cardiac surgery. Different levels of skills and surgeon's performance may play a role in this finding.

Shorter CBP and XC time were reported by others, where sutureless or rapid deployment bioprosthesis was implanted exclusively in all minimally invasive AVR cases. (23, 41, 42)

On the contrary, standard sutured prosthetic valves and implant techniques were utilized in all cases in our study. This inconsistency in the literature may be secondary to surgical experience, heterogenicity of less invasive approaches, center volume or the use of rapid deployment and sutureless valves. In this study, longer pump time was associated with an increased incidence of blood product transfusion.

3.2.2.2 Post-operative complications

The standard AVR is a well-established procedure with proven safety with excellent clinical outcomes. The Society of Thoracic Surgeons reported an overall 30-day mortality rate of 2.6% and a stroke rate of 1.4% following isolated AVR. (43, 44) Despite the potential benefits of a

minimally invasive approach, it has to produce equivocal or superior outcomes than the standard approach.

3.2.2.2.1 Cerebrocardiovascular accident and atrial arrhythmias

The risk of cerebrocardiovascular accident due to improper de-airing with limited access and the development of postoperative AF may increase in the MSAVR group. However, a recent meta-analysis of propensity-matched studies comparing the two techniques found no differences in the incidence of postoperative CVA.(22) These results are consistent with data obtained in the present research, where the rate of CVA is not significant between the groups (FSAVR 1.3%, MSAVR 1.9%, p=0.64). While postoperative atrial arrhythmias' etiology remains complex and multi-factorial, many studies demonstrated a reduction in new-onset AF or atrial arrhythmias in less invasive AVR. (35, 45-47) On the contrary, we did not demonstrate a reduction in atrial arrhythmia development.

3.2.2.2.2 High-risk patients with pre-existing renal dysfunction and the incidence of postoperative renal dialysis

The presence and development of chronic kidney disease are often associated with valvular heart disease, including aortic stenosis. (48, 49)Approximately 28% to 55% of patients with end-stage renal disease (ESRD) have early onset of aortic valve calcification, 10 to 20 years earlier than the general population. Moreover, in those patients with ESRD patients, aortic stenosis progresses more rapidly with an annual decrease in aortic valve area of 0.23 cm^2 per year compared with 0.05 cm^2 to 0.1 cm^2 per year in non-uremic patients. The presence of renal dysfunction may increase surgical morbidity and mortality. (50)In this study, the MSAVR group had a higher incidence of pre-existing renal failure, though not statistically significant. In our study, despite the higher incidence of pre-existing renal impairment in the MSAVR group, there was no increased need for

postoperative dialysis between the groups. In other words, MSAVR is safe even in patients with poor renal function and is not associated with an increased risk of dialysis. These findings align with results obtained from meta-analysis and other retrospective studies.(21, 40, 51)

3.2.2.2.3. 30-day mortality and long-term survival

Due to the complexity of the minimally invasive AVR, aortic cross-clamp and cardiopulmonary bypass times were longer in comparison with the standard approach. This may lead to prolonged myocardial ischemic time and may negatively impact clinical outcomes, short and long-term survival. Nonetheless, several studies have demonstrated no significant difference in 30-day mortality or short and long-term survival rate between these approaches. (14, 52)Our center 30-day mortality is excellent and low with an overall rate of 0.5%, compare to 2.6% reported by STS. We reported only four deaths in the FSAVR and one death in the MSAVR cohort and not significantly different between the two groups (p=0.79).

No significant difference was observed in long-term survival between groups in both Kaplan-Meier analysis and univariate Cox proportional hazards regression model. In the Kaplan-Meier analysis, the long-term survival of FSAVR and MSAVR follows an almost identical pattern. Each group had a survival rate higher than 80% at 4 years, and at least 70% survived up to 6 years. At 10 years, the survival rate of each group is higher than 50%. Since the cumulative incidence curve does not get to 50% or above, then the median survival time cannot be computed from this data. Older age, male gender, low BMI, low preoperative Hgb, pre-existing liver disease, renal dysfunction, COPD and pulmonary hypertension were independent risk factors negatively affecting the long-term survival in the multivariate Cox regression model.

3.2.2.2.4 Length of hospital stay

MSAVR preserves the sternum and rib cage integrity, which leads to quicker improvement in respiratory function and allows early mobilization, resulting in early extubation, shorter ICU stay, and collectively shorter hospital stay. In our cohort, the length of stay in hospital in the MSAVR group was significantly shorter. This finding also accords with other studies, which showed a reduction in time spent in hospital for the less invasive group. (53, 54)Advanced age contributed to a significant increase in hospital LOS. Interestingly, the female gender tends to stay for a shorter time in the hospital.

Chapter 4: Conclusion

4.1 Summary

Despite the reported benefits of minimally invasive AVR, widespread adoption has not occurred in BC and some skeptics call for stronger evidence. We present robust data on a cohort of BC patients who had aortic valve replacement via mini-sternotomy and full sternotomy in our institution over a decade.

As blood loss and requirement of blood product transfusion is an unavoidable part of cardiac surgery, blood product transfusion is associated with an increase in postoperative morbidly and mortality. Every effort to lower blood product transfusion should be made. Blood product transfusion rate is a strong indicator for procedural quality and safety. One of the more significant finding of this study is that MSAVR is associated with decreasing need for blood product transfusion and risk for reopening for bleeding.

Moreover, patients undergoing isolated AVR via a mini sternotomy have a shorter hospital length of stay with comparable short-term clinical outcomes and 30-day mortality. Although this study did not include financial impact analysis, one can postulate that with shorter hospital LOS and less blood product transfusion, MSAVR will positively impact resource utilization.

This study provides contemporary data on isolated AVR patients at our institution. To the best of our knowledge, it is the first study investigating the outcome of MSAVR in a Canadian setting. We have validated that the mini sternotomy is an effective alternative to the standard approach for aortic valve replacement. It is proven to be a safe and effective treatment for aortic stenosis with decrease in blood product transfusion, and hospital length of stay with equivalent 30-day mortality and long-term survival. It is also safe in high-risk patients such as those with renal impairment

without increasing their post-operative dialysis risk. It should be considered as part of the armamentarium of cardiac surgeon in the modern era.

4.2 Limitations

This study is limited as it was a single-centre, single surgeon experience in a retrospective manner. Moreover, surgeons who performed the cases for each procedure were different, adding an uncontrolled confounder. Considering this study's retrospective nature, we performed an inverse probability of treatment weighting (IPTW) analysis using propensity scoring. Since this cohort is not large enough and the study groups had comparable baseline characteristics, the propensity analysis has added no value to the result, thus standard statistical analysis was conducted. A larger sample size is required for better generalization of results. The current study lacked assessment of patient satisfaction, postoperative pain and cost-effectiveness analysis, which are also important outcomes that need to be further researched.

4.3 Future directions and recommendations

- This thesis has provided a more in-depth insight into the clinical outcome of mini-sternotomy AVR compared to the standard technique. Before this study, the benefit and effectiveness of MSAVR was purely anecdotal. The results are auspicious despite the small sample size in the MSAVR group. Although we advocate for the less invasive approach, there is a need for a well-constructed, adequately powered prospective randomized controlled study comparing MSAVR with FSAVR.
- A future study investigating patient reported outcomes would be fascinating. As long as there is equipoise considering the traditional morbidity and mortality measures, the debate

between sternotomy based and minimally invasive aortic valve replacement may never be settled otherwise. Quality of life indicators such as patient stratification, pain score, return to daily living and physical activity are highly valued for patient and often under-appreciated by caregivers. Study for these outcomes is much needed, especially with the growing number of elderly patients in our surgical practice.

- As there are many novel valve prostheses and enabling technology for less invasive surgery in general, it would be interesting to assess their impact on minimally invasive AVR.
- Regarding the current study, we aim to increase the study period beyond 2016 to obtain a larger sample size, thus improving the power and may further demonstrate the beneficial effects of MSAVR.

Bibliography

1. Weinhaus AJ, Roberts KP. Anatomy of the human heart. Handbook of Cardiac Anatomy, Physiology, and Devices: Second Edition. 2005:59-85.
2. Cohn LH. Cardiac surgery2008. 376-85 p.
3. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368(9540):1005-11.
4. Thaden JJ, Nkomo VT, Enriquez-Sarano M. The global burden of aortic stenosis. (1873-1740 (Electronic)).
5. Iung B, Vahanian A. Epidemiology of acquired valvular heart disease. (1916-7075 (Electronic)).
6. Hess OM, Ritter M, Schneider J, Grimm J, Turina M, Krayenbuehl HP. Diastolic stiffness and myocardial structure in aortic valve disease before and after valve replacement. Circulation. 1984;69(5):855-65.
7. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, et al. Prospective study of asymptomatic valvular aortic stenosis: Clinical, echocardiographic, and exercise predictors of outcome. Circulation. 1997;95(9):2262-70.
8. Frank S, Johnson A, Ross J. Natural history of valvular aortic stenosis. British Heart Journal. 1973;35(1):41-6.
9. Greve AM, Boman K, Gohlke-Baerwolf C, Kesäniemi YA, Nienaber C, Ray S, et al. Clinical implications of electrocardiographic left ventricular strain and hypertrophy in asymptomatic patients with aortic stenosis: The simvastatin and ezetimibe in aortic stenosis study. Circulation. 2012;125(2):346-53.
10. Selzer A. Changing Aspects of the Natural History of Valvular Aortic Stenosis. 1987. p. 91-8.
11. Marquis-Gravel G, Redfors B, Leon MB, Généreux P. Medical Treatment of Aortic Stenosis. (1524-4539 (Electronic)).
12. Nishimura RA, O'Gara PT, Bavaria JE, Brindis RG, Carroll JD, Kavinsky CJ, et al. 2019 AATS/ACC/ASE/SCAI/STS Expert Consensus Systems of Care Document: A Proposal to Optimize Care for Patients With Valvular Heart Disease: A Joint Report of the American Association for Thoracic Surgery, American College of Cardiology, American Society o. Journal of the American College of Cardiology. 2019;73(20):2609-35.
13. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. Journal of the American College of Cardiology. 2017;70(2):252 LP-89.
14. Brown JM, O'Brien SM, Wu C, Ann J, Sikora H, Griffith BP, et al. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: Changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. The Journal of Thoracic and Cardiovascular Surgery. 2008;137:82-90.
15. Badhwar V, Rankin JS, Jacobs JP, Shahian DM, Habib RH, D'Agostino RS, et al. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2016 Update on Research. (1552-6259 (Electronic)).
16. Rao PN, Kumar AS. Aortic valve replacement through right thoracotomy. (0730-2347 (Print)).
17. Cosgrove DM, Sabik JF. Minimally invasive approach for aortic valve operations. Ann Thorac Surg. 1996;62:596-7.
18. STS National Database Spring 2003, Executive Summary. Duke Clinical Research Institute, Durham, NC 2003.
19. Rosengart TK, Feldman T Fau - Borger MA, Borger Ma Fau - Vassiliades TA, Jr., Vassiliades Ta Jr Fau - Gillinov AM, Gillinov Am Fau - Hoercher KJ, Hoercher Kj Fau - Vahanian A, et al. Percutaneous and minimally invasive valve procedures: a scientific statement from the American Heart Association Council on Cardiovascular Surgery and Anesthesia, Council on Clinical Cardiology, Functional Genomics

and Translational Biology Interdisciplinary Working Group, and Quality of Care and Outcomes Research Interdisciplinary Working Group. (1524-4539 (Electronic)).
20. Cosgrove DM, Sabik JF. Minimally invasive approach for aortic valve operations. Ann Thorac Surg. 1996;62.
21. Aliahmed HMAA, Karalius R, Valaika AAAAAA, Grebelis A, Semeniene P, Cypiene R, et al. Efficacy of aortic valve replacement through full sternotomy and minimal invasion (Ministernotomy). Medicina (Lithuania). 2018;54(2):1-12.
22. Shehada S-E, Elhmidi Y, Mourad F, Wendt D, Gabry ME, Benedik J, et al. Minimal access versus conventional aortic valve replacement: a meta-analysis of propensity-matched studies †. Interactive CardioVascular and Thoracic Surgery 25. 2017.
23. Mazine A, Teoh K, Bouhout I, Bhatnagar G, Pelletier M, Voisine P, et al. Sutureless aortic valve replacement: A Canadian multicentre study. Canadian Journal of Cardiology. 2015;31(1):63-8.
24. Soppa G, Yates M, Viviano A, Smelt J, Valencia O, van Besouw JP, et al. Trainees can learn minimally invasive aortic valve replacement without compromising safety. Interactive Cardiovascular and Thoracic Surgery. 2015;20(4):458-62.
25. Svensson LG, Adams DH, Bonow RO, Kouchoukos NT, Miller DC, O'Gara PT, et al. Aortic valve and ascending aorta guidelines for management and quality measures. Annals of Thoracic Surgery. 2013;95(6 SUPPL.).
26. Bonacchi M, Prifti E, Giunti G, Frati G, Sani G, Surgery C, et al. Does ministernotomy improve postoperative outcome in aortic valve operation? A prospective randomized study. Annals of Thoracic Surgery. 2002;73(2):460-5.
27. Kempfert J Fau - Mohr FW, Mohr Fw Fau - Walther T, Walther T. Minimally invasive aortic valve surgery: where now and where to next? (1744-8344 (Electronic)).
28. Khoshbin E, Prayaga S, Kinsella J. Mini-sternotomy for aortic valve replacement reduces the length of stay in the cardiac intensive care unit: meta-analysis of randomised controlled trials. BMJ Open. 2011;1:266-.
29. Modi P, Hassan A Fau - Chitwood WR, Jr., Chitwood WR, Jr. Minimally invasive mitral valve surgery: a systematic review and meta-analysis. (1873-734X (Electronic)).
30. Murphy GJ, Reeves Bc Fau - Rogers CA, Rogers Ca Fau - Rizvi SIA, Rizvi Si Fau - Culliford L, Culliford L Fau - Angelini GD, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. (1524-4539 (Electronic)).
31. Velasquez CA, Singh M, Bin Mahmood SU, Brownstein AJ, Zafar MA, Saeyeldin A, et al. The Effect of Blood Transfusion on Outcomes in Aortic Surgery. Int J Angiol. 2017;26(3):135-42.
32. Engoren MC, Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ. Effect of blood transfusion on long-term survival after cardiac operation. Annals of Thoracic Surgery. 2002;74(4):1180-6.
33. Karkouti K. Transfusion and risk of acute kidney injury in cardiac surgery. British Journal of Anaesthesia. 2012;109(SUPPL1):i29-i38.
34. Mihaljevic T, Nowicki ER, Rajeswaran J, Blackstone EH, Lagazzi L, Thomas J, et al. Survival after valve replacement for aortic stenosis: Implications for decision making. Journal of Thoracic and Cardiovascular Surgery. 2008;135(6).
35. Neely RC, Boskovski MT, Gosev I, Kaneko T, McGurk S, Leacche M, et al. Minimally invasive aortic valve replacement versus aortic valve replacement through full sternotomy: the Brigham and Women's Hospital experience. Annals of cardiothoracic surgery. 2015;4(1):38-48.
36. Johnston DR, Atik FA, Rajeswaran J, Blackstone EH, Nowicki ER, Iii FS, et al. Outcomes of less invasive J-incision approach to aortic valve surgery. The Journal of Thoracic and Cardiovascular Surgery. 2012;144(4):852-8.e3.
37. Shehada S-eE, Öztürk Ö, Wottke M, Lange R. Propensity score analysis of outcomes following minimal access versus conventional aortic valve replacement. European Journal of Cardio-thoracic Surgery. 2016;49(2):464-70.

38. Kumar AB, Suneja M. Cardiopulmonary bypass-associated acute kidney injury. (1528-1175 (Electronic)).
39. Vukovic PM. The role of ministernotomy in aortic valve surgery — A prospective randomized study. 2019(January).
40. Glauber M, Ferrarini M, Miceli A. Minimally invasive aortic valve surgery: state of the art and future directions. Annals of cardiothoracic surgery. 2015;4(1):26-32.
41. Dalen M, Biancari F, Rubino AS, Santarpino G, Glaser N, De Praetere H, et al. Aortic valve replacement through full sternotomy with a stented bioprosthesis versus minimally invasive sternotomy with a sutureless bioprosthesis. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2016;49(1):220-7.
42. Oezpeker C, Barbieri F, Zujs V, Grimm M, Lio A, Glauber M, et al. Minimally Invasive Redo-Aortic Valve Replacement: Reduced Operative Times as Compared to Full Sternotomy. Thorac Cardiovasc Surg. 2020;68:141-7.
43. Badhwar V, Rankin JS, Jacobs JP, Shahian DM, Habib RH, D'Agostino RS, et al. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2016 Update on Research. Annals of Thoracic Surgery. 2016;102(1):7-13.
44. Badhwar V, Rankin JS, Thourani VH, D'Agostino RS, Habib RH, Shahian DM, et al. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2018 Update on Research: Outcomes Analysis, Quality Improvement, and Patient Safety. (1552-6259 (Electronic)).
45. Mächler HE, Bergmann P, Anelli-Monti M, Dacar D, Rehak P, Knez I, et al. Minimally invasive versus conventional aortic valve operations: a prospective study in 120 patients. Ann Thorac Surg. 1999;67(4):1001-5.
46. Miceli A, Gilmanov D, Murzi M, Marchi F, Ferrarini M, Cerillo AG, et al. Minimally invasive aortic valve replacement with a sutureless valve through a right anterior mini-thoracotomy versus transcatheter aortic valve implantation in high-risk patients. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2016;49(3):960-5.
47. Gilmanov D, Bevilacqua S, Murzi M, Cerillo AG, Gasbarri T, Kallushi E, et al. Minimally invasive and conventional aortic valve replacement: a propensity score analysis. The Annals of thoracic surgery. 2013;96(3):837-43.
48. Straumann E, Meyer B, Misteli M, Blumberg A, Jenzer HR. Aortic and mitral valve disease in patients with end stage renal failure on long-term haemodialysis. British Heart Journal. 1992;67(3):236-9.
49. London GM, Pannier B Fau - Marchais SJ, Marchais Sj Fau - Guerin AP, Guerin AP. Calcification of the aortic valve in the dialyzed patient. (1046-6673 (Print)).
50. Thourani VH, Keeling WB, Sarin EL, Guyton RA, Kilgo PD, Dara AB, et al. Impact of Preoperative Renal Dysfunction on Long-Term Survival for Patients Undergoing Aortic Valve Replacement. ATS. 2011;91:1798-807.
51. Furukawa N, Kuss O, Aboud A, Schönbrodt M, Renner A, Hakim meibodi K, et al. Ministernotomy versus conventional sternotomy for aortic valve replacement: Matched propensity score analysis of 808 patients. European Journal of Cardio-thoracic Surgery. 2014;46(2):221-7.
52. Shehada S-E, Elhmidi Y, Mourad F, Wendt D, Gabry ME, Benedik J, et al. Minimal access versus conventional aortic valve replacement: a meta-analysis of propensity-matched studies †. Interactive cardiovascular and thoracic surgery. 2017;25(4):624-32.
53. Aris A, Ca ML, Delgado LJ, Gala J. ORIGINAL ARTICLES : CARDIOVASCULAR Ministernotomy Versus Median Sternotomy for Aortic Valve Replacement : A Prospective , Randomized Study. 1999;4975(99).
54. Carabello BA, Paulus WJ. Aortic stenosis. The Lancet. 2009;373(9667):956-66.

Appendices

Appendix A Data analysis after inverse probability of treatment weighting (IPTW) using the propensity score

Table 10. Baseline characteristics of unmatched patients undergoing minimally invasive and conventional aortic valve replacement

Variable	FSAVR (n=776)	MSAVR (n=134)	*p* value	SMD	SMDW
Age (year)	69.67 ± 12.19	70.67 ± 11.84	0.38	8.36	-2.20
BMI (kg/m2)	28.60 ± 5.89	28.83 ± 6.03	0.69	3.74	0.85
Body surface area	1.90 (1.80,2.10)	2.00 (1.80,2.10)	0.64	2.03	4.37
Preop hemoglobin (g/L)	133.74 ± 18.05	134.80 ± 16.61	0.53	2.03	4.37
Preop platelet	198 (164, 241)	210 (168, 267)	0.09	-23.2	-6.5
Female gender	323 (41.6)	60 (44.8)	0.50	6.37	-14.29
LV ejection fraction (<50%)	226 (29.1)	22 (16.4)	0.002	30.65	-7.69
NYHA Class III\IV	382 (49.3)	103 (77.5)	<.001	59.76	-5.41
CCS			0.020	-17.24	1.17
Class 1	47 (6.1)	14 (10.4)			
Class 2	159 (20.6)	15 (11.2)			
Class 3	83 (10.7)	16 (11.9)			
Class 4	24 (3.1)	1 (0.7)			
Hypertension	563 (72.9)	108 (80.6)	0.06	18.24	-14.69
Diabetes	181 (23.3)	36 (26.9)	0.37	8.17	-2.24
Smoking within one month	55 (7.1)	12 (9)	0.44	6.94	-5.35
Prior MI	72 (9.3)	14 (10.4)	0.67	3.92	3.73
Chronic steroid use	12 (1.6)	3 (2.2)	0.57	5.02	-2.96
Liver disease	97 (12.6)	13 (9.7)	0.35	-9.11	-14.35
Renal dysfunction (eGFR <60, >15)	138 (17.9)	21 (16)	0.60	-4.98	-14.99
Renal failure (eGFR <15)	68 (8.8)	17 (12.7)	0.15	12.71	2.66
Dialysis	15 (1.9)	4 (3)	0.43	6.80	4.40
COPD	173 (22.3)	26 (19.4)	0.46	-7.12	-8.30
Pulmonary hypertension	123 (15.9)	26 (19.4)	0.32	9.11	2.30
Coagulopathy (hyper & hypo)	11 (1.4)	2 (1.5)	0.95	0.56	6.49

CCS: Canadian Cardiovascular Society grading of angina pectoris; NYHA: New York Heart Association. MI: myocardial infarction; COPD: chronic obstructive pulmonary disease. Values shown as mean ± SD, or median (Q1, Q3), or n (%). Q1, Q3: 1st and 3rd quartile. Percentages calculated with complete observations. P values are obtained using t test, or Wilcoxon rank test for continuous variables, Chi-Square test for categorical variables. SMD and SMDW: standardized mean difference before and after inverse probability of treatment weighting (IPTW) using the propensity score, respectively.

Table 11. Summary of blood product transfusion by surgical type (after IPTW)

Variables	All (n=910)	FAVR (n=776)	MSAVR (n=134)	*p* value ‡
Blood transfusion				<0.001
No	468 (52.6)	379 (50.2)	89 (66.9)	
Yes	421 (47.4)	377 (49.8)	44 (33.1)	
Unit of numbers transfused, mean ± SD†	5.3 ± 6.6	5.3 ± 6.7	5.0 ± 5.1	0.97
Unit of numbers transfused, median (q1, q3) †	3.0 (2.0, 6.0)	3.0 (2.0, 6.0)	3.0 (2.0, 7.0)	
Reoperation for bleeding				0.23
No	868 (97.8)	736 (97.5)	132 (99.3)	
Yes	20 (2.2)	19 (2.5)	1 (0.7)	

Values shown as n (%) if not specified. Calculation based on complete data† Mean or median calculated based on the sum of blood product counts for the 421-patient receiving blood transfusion. ‡ P values are obtained using weighted logistic regression between incision type and the variables listed in this table.

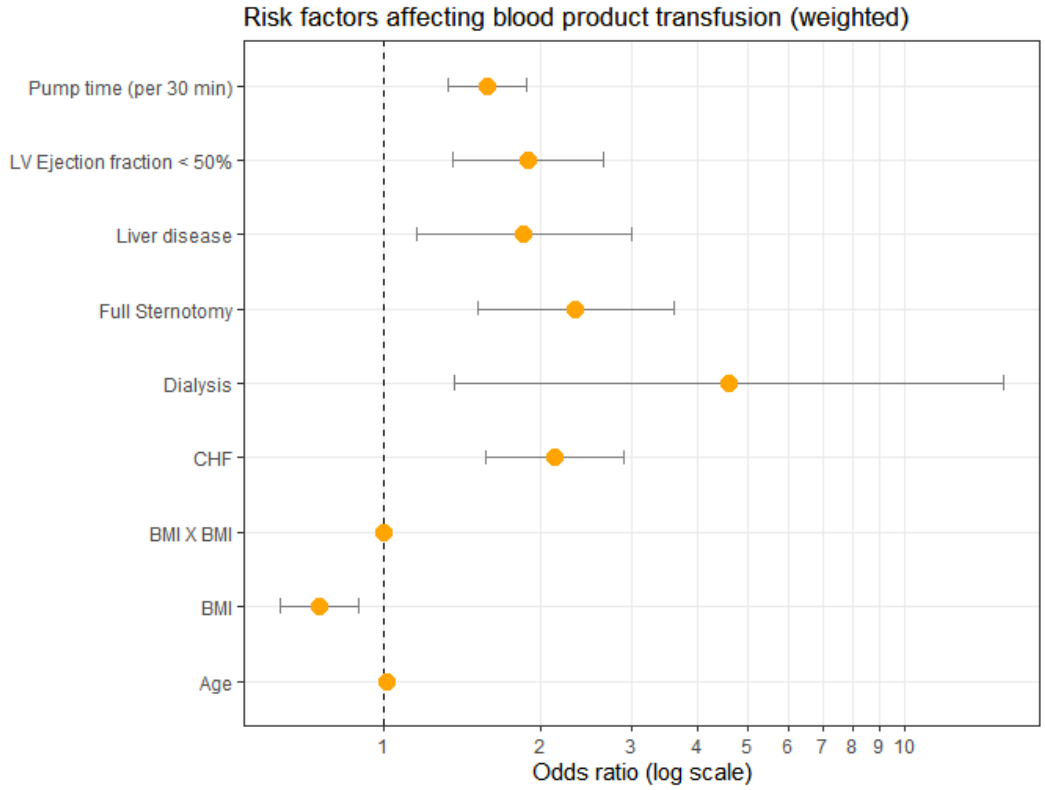

Figure 10. Forest plot of Odds ratio from multivariate logistic regression analysis (after IPTW)

Table 12. Logistic regression analysis on blood transfusion (after IPTW)

Paramters	Univariate analysis		Multivariate analysis	
	Odds Ratio (95% CI)	***p* value**	**Odds Ratio (95% CI)**	***p* value**
Full sternotomy	1.957 (1.328 – 2.882)	<0.001	2.340 (1.516 – 3. 612)	<0.001
Age (years)	1.023 (1.011 – 1.034)	<0.001	1.018 (1.006 – 1.031)	0.004
Female gender	1.180 (0.903 – 1.542)	0.23		
BMI (kg/m^2)	0.951 (0.929 – 0.974)	<0.001	0.754 (0.634 – 0.898)	0.002
BMI^2	–	–	1.004 (1.001 – 1.006)	0.009
LV ejection fraction (< 50%)	1.548 (1.150 – 2.083)	0.004	1.896 (1.358 – 2.647)	<0.001
Prior MI	1.539 (0.985 – 2.405)	0.06		
Liver disease	2.671 (1.720 – 4.148)	<0.001	1.854 (1.155 – 3.008)	0.011
Renal dysfunction	1.484 (1.042 – 2.115)	0.029		
Dialysis	5.237 (1.646 – 16.67)	0.005	4.618 (1.372 – 15.54)	0.014
COPD	1.552 (1.124 – 2.143)	0.008		
Pulmonary hypertension	1.490 (1.046 – 2.122)	0.027		
CHF	1.993 (1.525 – 2.605)	<.001	2.134 (1.568 – 2.903)	<0.001
Pump time (per 30 min)	1.486 (1.276 – 1.732)	<.001	1.583 (1.335 – 1.877)	<0.001

The multiple logistic regression model was generated using backwards selection algorithm with statistical significance of inclusion and exclusion at $p<0.05$ and variables selected using clinical judgement. Firth's penalized likelihood approach was used. P value =0.24 from Hosmer and Lemeshow Goodness-fit-fit test showed that the model selected is suitable and final c statistic is 0.72. BMI^2 =BMI * BMI. CI = confidence interval.

Table 13. Clinical outcomes of patients underwent FSAVR and MSAVR at St. Paul's Hospital (after IPTW)

Variable	FSAVR (n=776)	MSAVR (n=134)	*p* value
Pump time (min)	84.5 ± 29.7	76.3 ± 15.0	0.002
Clamp time (min)	64.9 ±24.5	60.3 ± 13.7	0.041
Discharge hemoglobin (g/L)	106.6 ± 13.9	109.6 ± 14.2	0.022
Discharge platelet	191.0(150.0,261.0)	176.0(140, 242.0)	0.05
Discharge INR	2.0 (1.5, 2.2)	1.6 (1.2,1.9)	0.010
Prosthesis type			0.30
Bioprosthetic	543 (94.2)	108 (91.6)	
Mechanical	34 (5.8)	10 (8.4)	
Length of stay in hospital (days)	8.7 ± 7.2	7.1 ± 6.0	0.020
Sternum wound infection	6 (0.9)	0 (0.0)	0.97
Reoperation for hemorrhage/tamponade	11 (1.9)	2 (2.3)	0.79
Arrhythmia - atrial	275 (45.2)	39 (42.3)	0.60
CVA	8 (1.3)	1 (1.1)	0.87
New hemodialysis	15 (2.5)	2 (1.6)	0.59
Prolonged ventilation	63 (10.4)	7 (7.8)	0.44

Comments: Values shown as mean±sd, or median (Q1, Q3), or n (%). Q1, Q3: 1st and 3rd quartile. Percentages calculated with complete observations. P values are obtained using weighted logistic regression between incision type and the variables listed in this table.

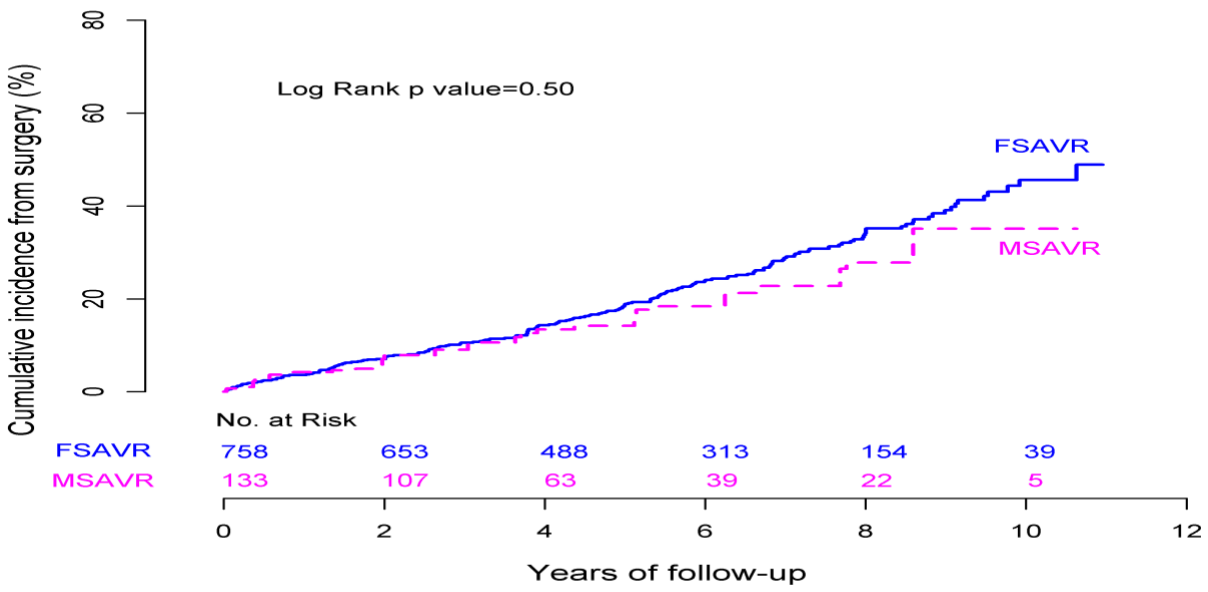

Figure 11. Kaplan-Meier curve of long-term survival following FSAVR and MIAVR (after IPTW)

Table 14. Cox PH regression analysis for long term survival post AVR (After IPTW)

	Univariate model		Multivariate model	
Parameter	**Hazard ratio (95% CI)**	***p* value**	**Hazard ratio (95% CI)**	***p* value**
Incision type	0.812 (0.526, 1.253)	0.35	1.083 (0.696, 1.684)	0.72
Age (year)	1.065 (1.049, 1.080)	<0.001	1.055 (1.039, 1.072)	<0.001
Female gender	1.294 (0.992, 1.688)	0.06	0.738 (0.552, 0.988)	0.041
BMI	0.994 (0.970, 1.018)	0.60	0.802 (0.714, 0.901)	<0.001
BMI^2	—	—	1.004 (1.002, 1.005)	<0.001
Preop hemoglobin (g/L)	0.972 (0.965, 0.978)	<0.001	0.980 (0.972, 0.988)	<0.001
Liver disease	1.710 (1.219, 2.400)	0.002	1.517 (1.068, 2.155)	0.020
Renal dysfunction	2.799 (1.937, 4.045)	<0.001	1.760 (1.186, 2.610)	0.005
COPD	1.970 (1.483, 2.615)	<0.001	1.410 (1.051, 1.891)	0.022
Pulmonary hypertension	2.257 (1.682, 3.029)	<0.001	1.797 (1.335, 2.419)	<0.001
NYHA (III+IV)	1.872 (1.413, 2.480)	<0.001		
LV ejection fraction (<50%)	1.036 (0.776, 1.383)	0.81		
Hypertension	1.902 (1.330, 2.720)	<0.001		

Comments: The model results listed in Table 4 were obtained by stepwise selection method with entry probability 0.25 and stay probability 0.15 using all the variables listed in Table 3. BMI^2=BMI*BMI. COPD: chronic obstructive pulmonary disease. CI: confidence interval.

Table 15. The regression model for the predictors of longer hospital stays following AVR (after IPTW)

Parameter	Estimate	Standard Error	Wald 95% Confidence Limits		*p* value
Incision type (mini)	-0.112	0.057	-0.225	0	0.05
Age (year)	0.009	0.002	0.006	0.013	<0.001
Female gender	-0.074	0.041	-0.155	0.007	0.07
Preop hemoglobin (g/L)	-0.005	0.001	-0.007	-0.003	<0.001
LV ejection fraction (<50%)	0.104	0.043	0.0196	0.188	0.016
NYHA (III+IV)	0.092	0.041	0.012	0.172	0.025
CCS*					
Class 1	-0.027	0.076	-0.177	0.123	0.72
Class 2	-0.054	0.052	-0.156	0.047	0.29
Class 3	0.006	0.062	-0.116	0.127	0.93
Class 4	0.449	0.106	0.241	0.657	<0.001
Liver disease	0.159	0.058	0.045	0.273	0.006
Renal dysfunction	0.167	0.070	0.029	0.305	0.018
Dialysis	0.297	0.137	0.028	0.565	0.031
COPD	0.128	0.047	0.038	0.218	0.005
Pulmonary hypertension	0.118	0.051	0.019	0.218	0.020

Comments: Since the mean is far different from its variance, a negative binomial distribution is assumed for the length of stay in hospital, see the results in Table 3 and Table 4. Backwards selection method used with probability 0.10 using all the variables listed in Table 2. * Reference: CCS='None'. COPD: chronic obstructive pulmonary disease.