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Propensity Score Analysis of Outcomes following Minimally Invasive versus Conventional Aortic Valve Replacement

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To my Parents,

To my Sisters,

To my Brothers,

To my Country

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List of Abbreviations

ABGs	Arterial blood gases
ACC/AHA	American College of Cardiology/American Heart Association
AI	Aortic insufficiency
AF	Atrial fibrillation
AR	Aortic regurgitation
AS	Aortic stenosis
ASD	Atrial septal defect
AV	Aortic valve
AVA	Aortic valve area
AVR	Aortic valve replacement
AVB	Atrioventricular block
CAD	Coronary artery disease
CABG	Coronary artery bypass grafting
CAVR	Conventional aortic valve replacement
CHF	Congestive heart failure
CI	Cardiac index
CO	Cardiac output
CPB	Cardiopulmonary bypass
CPR	Cardiopulmonary resuscitation
CT	Computed tomography
CVA	Cerebrovascular accident
CVC	Central venous catheter
DRGs	Diagnosis related groups
ECC	Extracorporeal circulation
ECG	Electrocardiogram
EF	Ejection fraction
HR	Heart rate
IQR	Inter Quartile Range
LDL	Low density lipoprotein
LV	Left ventricle

LVEDD	Left ventricular end-diastolic diameter
LVEDP	Left ventricular end-diastolic pressure
LVEDV	Left ventricular end-diastolic volume
LVF	Left ventricular function
LVH	Left ventricular hypertrophy
LVOT	Left ventricular outlet
LVOTO	Left ventricular outlet obstruction
MIAVR	Minimal invasive aortic valve replacement
MR	Mitral regurgitation
MRI	Magnetic resonance imaging
MS	Mitral stenosis
NG	Nasogastric
NIV	Non-invasive ventilation
PFO	Patent foramen oval
PO	Per oral
PS	Pulmonary valve stenos
RIMA	Right internal mammary artery
SAV	Supraannular valve
SD	Standard Deviation
SJM	St. Jude Medical
SV	Stroke volume
SVC	Superior vena cava
TAVI	Transcatheter aortic valve implantation
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
TR	Tricuspid regurgitation
TS	Tricuspid stenosis
TTE	Transthoracic echocardiography
VAJ	Ventriculoarterial Junction
VSD	Ventricular septal defect

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1. Introduction

1.1 Anatomy of the Aortic Valve

1.1.1 Descriptive Anatomy

Aortic valve is a semi-lunar valve located between the left ventricle and the aorta at the left ventricle outflow tract. It consists of 3 leaflets (cusps) attached to the aorta at 3 points known as commissures. The space between the free edge and each leaflet is known as sinus of Valsalva. The coronary arteries arise from two of the three sinuses. Accordingly, the respective cusps are named the right coronary, the left coronary and the non-coronary (posterior) cusp. The ostia of the coronaries are located at the upper part of the sinuses and the ostium of the right coronary is slightly higher than the left one (Lawrence H. Cohn, 2012; Kirklin & Kouchoukos, 2003).

1.1.2 Surgical Anatomy

The area near the left-posterior commissure is the fibrous continuity, which interconnects the aorta and the mitral valve annulus. The area beneath this commissure is defined as the aorto-mitral curtain. The posterior cusp attaches above the posterior diverticulum of the LVOT and opposes the right atrial wall. The right-posterior commissure is located directly above the atrioventricular bundle and the membranous septum. The right-left commissure opposes the posterior commissure of the pulmonary valve and the two associate cusps oppose the right ventricular infundibulum. The lateral part of the left coronary artery is the only part of the aortic valve which has no close relation to any other heart chamber and has an indirect relation to the free pericardial space (Lawrence H. Cohn, 2012; Kaiser, Kron, & Spray; Kirklin & Kouchoukos, 2003). (Figure1.1)

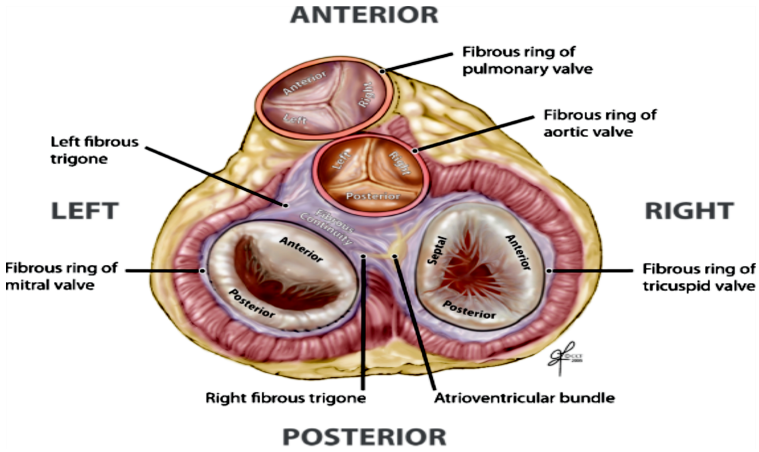

Figure 1. 1. Anatomical relationship between the aortic valve and the surrounding structures

(Source: Cohn LH: Cardiac Surgery in the Adult, 4th Edition (Lawrence H. Cohn, 2012)).

The attachment of the cusps to the left ventricle outflow tract is called aortic annulus. Due to the semilunar shape of the cusps, the aortic valve has a non-true annulus, but a crown-like ring attachment. The cusps have their semilunar attachment in the aortic root, a hollow cylinder placed between the left ventricular outflow tract and the tubular aorta. The distal border of the cuff is the sinotubular junction, which is the narrowest portion of the ascending aorta; it is defined as imaginary lines connecting the top of the commissures. The proximal border is the ventriculoarterial junction (VAJ), which has hemodynamic and anatomic parts. The hemodynamic part is marked by the semilunar attachments of the cusps, whereas the anatomical part is marked by the circular attachment of the proximal aorta, the muscular and membranous ventricular septum (Lawrence H. Cohn, 2012; Piazza et al., 2008). (Figure1.2)

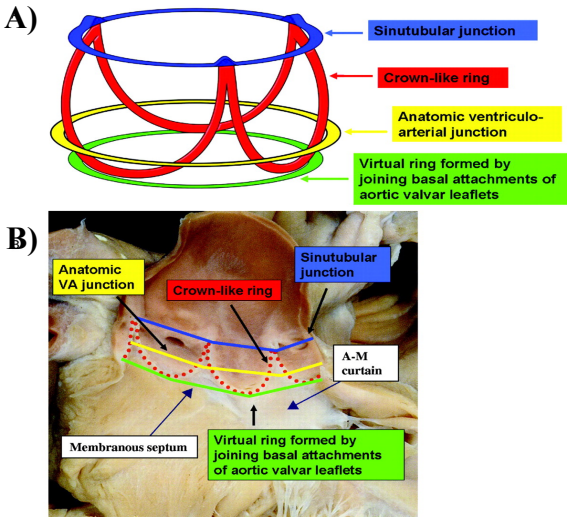

Figure 1. 2. Complex anatomy of the aortic valve (VA = ventriculoarterial, A-M = aortic-mitral)
A) Three-dimensional arrangement of the aortic root. B) The location of the 3 rings relative to the crown-like hinges of the cusps. (Source: Circ CardiovascIntervent. 2008; 1:74-81. (Piazza et al., 2008))

1.2 Physiology of the Aortic valve

The main function of the aortic valve is to allow blood flow from the left ventricle into the aorta and to prevent backflow of blood from the aorta into the left ventricle (Lawrence H. Cohn, 2012). Opening of the aortic valve is a passive movement of the aortic cusps, created by the pressure difference between the aorta and the left ventricle in association with compliance of the aortic root. The dynamic motion of the aortic root plays an important role in opening and closing the aortic valve. During late diastole, aortic root starts to expand due to filling the left ventricle with blood; root expansion is responsible for 20% of the cusps opening (Gnyaneshwar, Kumar, & Balakrishnan, 2002). As the pressure in the LVOT rises, the tension across the cusps decreases due to aortic root expansion. The loss of tension will lead to more dilatation of the aortic valve, which allows the valve to open rapidly at the start of the ejection (Mercer, 1973).

Closure of the aortic valve is an elegant mechanism, which recognizes the importance of the sinuses of Valsalva in valve closure. As ejection occurs, blood creates small eddy currents along the wall of the aorta allowing blood to drip into the sinuses of Valsalva. This leads to an expansion of the cusps away from the aortic wall and towards the aortic axis. Due to small flow reversal forces, the cusps close completely when the pressure difference between the LVOT and the aorta subsides (Bellhouse & Reid, 1969).

1.3 Pathology of Aortic Valve Diseases

1.3.1 Aortic Valve Stenosis (AS)

1.3.1.1 Etiology

Aortic valve stenosis is the most common heart disease in developed countries. An observational echocardiographic study reported that about 2% of the population older than 65 years have isolated calcific AS, whereas 29% exhibit age related aortic valve sclerosis without stenosis (Nkomo et al., 2006). AS is more common in males and prevalence increases with age; Otto and colleagues reported prevalence of 1.3% in patients aged 65 to 75 years, 2.4% in patients aged 75 to 85 years and 4% in patients older than 85 years (Otto, Lind, Kitzman, Gersh, & Siscovick, 1999).

The most common causes of aortic valve stenosis are:

I. Degenerative AS: Calcification is the most common cause of AS in adults. It starts along the flexion lines at the base of the cusps and leads finally to immobilization of the cusps. The natural mechanical stress of the aortic valve leads to proliferative and inflammatory changes with lipid accumulation and infiltration of macrophages and T-lymphocytes, in a process similar to vascular atherosclerosis (Otto et al., 1999; Rajamannan, Gersh, & Bonow, 2003). According to that, risk factors of developing AS are same as those for vascular atherosclerosis (smoking, low density hyperlipidemia, systemic hypertension and diabetes mellitus). Therefore, coronary artery disease is frequently present in patients with AS. (Figure 1.3)

II. Bicuspid AS*:* Calcified bicuspid aortic valve (BAV) is the most common cause of congenital AS. About 2% of population has a BAV (Fedak et al., 2002) which typically calcifies in the fifth or sixth decade of life causing severe AS. Bicuspid AV induces turbulence of the flow leads to injury of the leaflets, fibrosis, increased rigidity and finally calcification and narrowing of the orifice. BAV stenosis is also frequently associated with a dilation of the ascending aorta. (Figure 1.4)

III. Rheumatic AS*:* Aortic valve stenosis caused by rheumatic diseases is considered as the least common cause of AS in western countries (Roberts, 1970). Due to rheumatic fever the valve leaflets undergoes edema, infiltration of lymphocytes, revascularization and finally fibrous thickening with fusion of the leaflets causing AS (Roberts & Ko, 2005).

1.3.1.2 Pathophysiology and Hemodynamics

In the early phases of AS, there are no or mild hemodynamic consequences due to valve orifice reduction from 3-4 cm² to 1.5-2 cm² (Otto et al., 1999). Later on, AS will produce significant obstruction in the LVOT flow with increase in the LV pressure and the ejection time and increase in the wall stress resulting in left ventricular hypertrophy (LVH).

LV hypertrophy increases the myocardial oxygen consumption and leads to an increase in systolic pressure as well as prolonged ejection time. The prolonged ejection time will decrease the diastolic time and thus decrease the myocardial perfusion time. On the other hand, the increase in the diastolic pressure will result in increased endocardial compression of the coronary arteries and decease in coronary perfusion. Those two factors (decrease the myocardial perfusion time and decrease coronary blood flow) in addition to the increased oxygen demand of the hypertrophied ventricle will result in subendocardial ischemia, which may result in symptoms similar to angina pectoris and LV dysfunction (Marcus, Doty, Hiratzka, Wright, & Eastham, 1982).

The hypertrophied left ventricle will also be less complaint; the left ventricular end diastolic pressure (LVEDP) will increase. This will finally lead to a diastolic dysfunction with increase in atrial pressure for filling. Thus, atrial arrhythmia may develop and the patient may rapidly decompensate (Hess et al., 1984). At this stage, aortic valve replacement (AVR) would only partially remodel the severe hypertrophied LV and is associated with worse long term survival, even after initial successful surgery (Mihaljevic et al., 2008).

The severity of the AS can be assessed by measuring the aortic valve orifice area (AVA), mean pressure gradient and peak jet velocity. The normal AVA in adults is 2.5 to 3.5 cm². It is reduced in severe AS up to less than 1 cm² (Tardif et al., 1997). Transvalvular pressure gradient can be determined by pressure measurement in the left ventricle and proximal aorta. The peak-to-peak gradient results from the difference between peak LV pressure and peak aortic pressure. Measurement of the pressure gradient can be done invasively by cardiac catheterization, or non-invasively by echocardiography. The later can also assess the peak jet velocity through the AV.

1.3.1.3 Clinical Presentation

Symptoms: Patients with AS typically present with angina pectoris, syncope and symptoms of congestive heart failure (CHF): dyspnea, orthopnea and paroxysmal nocturnal dyspnea. The mechanisms of angina and CHF were mentioned above, but there is no clear mechanism for syncope. One theory postulates: " there is a decrease in brain perfusion during and after exercise in patients with severe AS due to the small outflow orifice (Schwartz, Goldfischer, Sprague, & Schwartz, 1969)". Late manifestations of AS might include atrial fibrillation and pulmonary hypertension.

Signs: Most common signs during auscultation are systolic crescendo decrescendos murmur which is loudest at the right upper border of the sternum or delay of the second heart sound (S2) due to prolonged ejection time. A classic pulsus parvus (small pulse) due to fall of stroke volume and systolic pressure, or a pulsus tardus (late pulse) due to prolonged ejection time could be diagnosed by palpation (Selzer, 1987).

Diagnostic tools*:* Cardiac catheterizations is helpful for the invasive diagnosis of the severity of AS. Echocardiography, computer tomography (CT) (Figure 1.3. and 1.4) and magnetic resonance imaging (MRI) are all non-invasive methods for the diagnosis of AS. Echocardiography plays the main role in diagnosis of aortic stenosis, due to its wide availability and lower cost in comparison to MRI and CT.

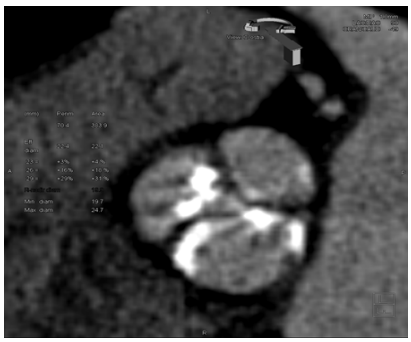

Figure 1. 3. CT scan showing calcified AS in tricuspid AV (axial plane)
(Source: Author collection from German Heart Center, Munich, Germany)

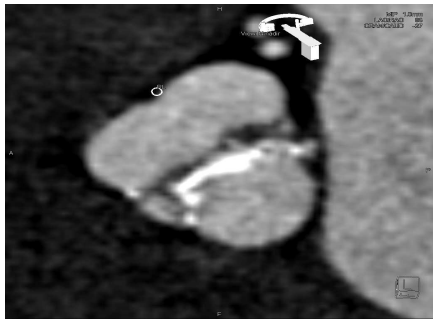

Figure 1. 4. CT scan showing calcified AS in bicuspid AV (axial plane)
(Source: Author collection from German Heart Center, Munich, Germany).

1.3.2 Aortic Valve Regurgitation (Insufficiency) (AR=AI)

1.3.2.1 Etiology

AR is seen most commonly in combination with AS due to calcific or rheumatic disease. In these patients, AR is primary caused by diseases, which affect the aortic cusps. Calcific and myxomatous degenerations, infective endocarditis, rheumatic disease or a bicuspid valve can all cause distortion of the aortic valve leaflets resulting in improper coaptation (Carabello, 2001; Tonnemacher et al., 1987). The most common cause of isolated AR is aortic root dilation. This may result from dissection, trauma, and chronic hypertension, bacterial or viral aortitis or in case of connective tissue disorders (e.g. Marfan's syndrome, Reiter's disease, Ehlers-Danlos syndromes and rheumatoid arthritis). All will result in improper leaflet coaptation and AR (Carter, Sethi, Lee, & Edwards, 1971; Roldan, Chavez, Wiest, Qualls, & Crawford, 1998). AR due to root dilatation is more common than primary valve disease in patients undergoing AVR for pure AR (Roberts, Ko, Moore, & Jones, 2006).

1.3.2.2 Pathophysiology and Hemodynamics

Acute AR*:* Sudden onset due to aortic root dissection, trauma or endocarditis will result in sudden increase in the left ventricle end diastolic volume (LVEDV) which leads to increase in the LVEDP and in the left atrial and pulmonary venous pressure, resulting in different degrees of pulmonary edema (Rahimtoola, 1993). In presence of acute AR, two main compensatory mechanisms attempt to maintain an effective cardiac output (CO): an increase in the contractility (Frank-Starling mechanism) and an increase the heart rate (HR).

Chronic AR*:* Chronic AR has a slow onset and it is associated with different compensatory mechanisms. As in acute AR, the increase in LVEDV would lead to increase in the LVEDP resulting in increase in the myocyte length leading to a pattern of remodeling of the LV, known as eccentric hypertrophy and chamber enlargement. This will result in increase the total stroke volume (SV) and will maintain the forward stroke volume (which defined as total SV minus regurgitated volume) (Grossman, Jones, & McLaurin, 1975). Increased forward volume besides peripheral vasodilatation during any physiologic change (e.g. exercise) would decrease diastolic filling and decreases the regurgitating time and volume. This explains, why bradycardia and therapy with vasodilators and negative chronotropic agents should be avoided in AR (Slordahl & Piene, 1991). Thereafter a further increase in the afterload will cause afterload mismatch and

results in reduction of the LV function (LVF) (J. Ross, Jr., 1985). Myocardial ischemia will result from decease in the coronary perfusion or increase in the myocardial oxygen demand, leading to LV dysfunction. This increase in the LV muscle mass, wall tension and systolic ventricular pressure will lead to cell death and fibrosis resulting in systolic dysfunction and heart failure.

1.3.2.3 Clinical Presentation

***Symptoms**:* They depend on the acuity of onset, severity of the regurgitation and the compliance of the ventricle and aorta. In acute severe AR, patients will present with a life threatening cardiovascular collapse indicating emergent treatment. In chronic AR, patients usually remain asymptomatic until AR becomes severe due to the compensatory mechanisms. At this stage, they will present with palpitations, angina pectoris and signs of heart failure (DeGowin, Brown, Christensen, & DeGowin, 1994).

Signs: The classic auscultatory finding is an early diastolic, decrescendo, blowing murmur that is best heard at the left sternal border. Also auscultation of the femoral artery will detect pulse bisferiens "pistol shot sounds" (Traube sign). Palpation would detect a classic widened pulse pressure "water hammer pulse" (Corrigan pulse). Some other signs can be detected in patients with AR like head bobbing or nodding with each heartbeat (De Musset sign), capillary pulsations in the lips and fingers (Quincke pulses) and pulsations of the uvula (Müller sign) (DeGowin et al., 1994).

Diagnostic tools: Same as in AS, AR could be diagnosed invasively with cardiac catheterization, or non-invasively with echocardiography, CT or MRI. Echocardiography is considered the tool of choice in diagnosis of AR. It is a cheap and easily available investigation which can define the severity of the AR (by using two-dimensional (2D) echocardiography with Doppler-color flow mapping) (Figure 1.5), gives a good idea about the morphology of the aorta and the aortic valve, the size of the heart chambers and assessment of the left ventricular function (Bouchard et al., 1989). TEE is a more accurate way to measure the AVA and gives more information about the shape and morphological changes in the aortic valve (Blumberg et al., 1997). (Figure 1.6)

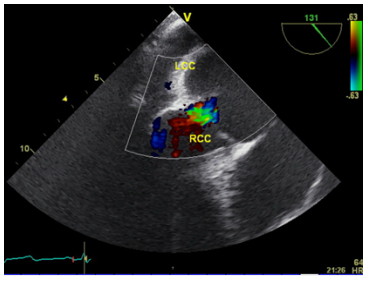

Figure 1. 5. TTE showing AR (long axis view)
(Source: Author collection from German Heart Center, Munich, Germany)

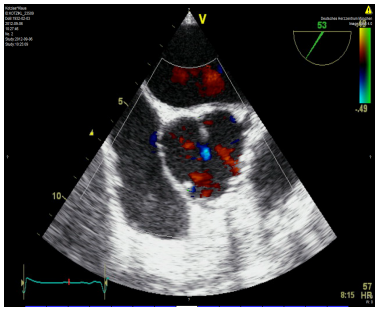

Figure 1. 6. TEE showing AR (short axis view)
(Source: Author collection from German Heart Center, Munich, Germany)

1.4 Management of Aortic Valve diseases

1.4.1 Management of Aortic Stenosis

1.4.1.1 Symptomatic Patients

Surgery is the definitive therapy for severe aortic stenosis. The onset of symptoms is the primary indication of AVR. Percutaneous balloon valvuloplasty (valvotomy) is only effective in congenital AS, and it is used in adults as a palliative measure or even as a bridge therapy before surgical intervention (American College of et al., 2006; Bonow et al., 2008; Otto, Kuusisto, Reichenbach, Gown, & O'Brien, 1994).

Medical therapy plays a secondary role in the therapy of AS. It is limited to lipid lowering medications, which may slow the progress of the disease, and treatment of CHF signs with diuretics and inotropes (American College of et al., 2006). Antibiotics are recommended for all patients who undergo dental or surgical procedures as a preventive strategy of endocarditis.

1.4.1.2 Asymptomatic Patients

Surgical AVR for asymptomatic patients with AS is still controversial. The 2006 ACA/AHA guidelines indicate AVR in asymptomatic patients with moderate to severe AS which is associated with reduced LVF or in cases of small AVA associated with LVH, since in such patients the disease rapidly progress to severe AS and they will require AVR surgery soon (American College of et al., 2006; Bonow et al., 2008). Pellikka and colleagues reported that survival rates would improve in patients with asymptomatic severe AS who underwent AVR, and sudden death from AS before onset of symptoms is estimated to be approximately 1% per year and the survival rate is dramatically reduced without surgical intervention (Pellikka et al., 2005).

1.4.2 Management of Aortic Regurgitation

1.4.2.1 Acute AR

Early surgery is indicated for this group of patients with repair or replacement of the valve depending on the etiology. Vasodilators, inotropic agents and CHF therapy are a temporarily treatment till surgery (American College of et al., 2006; Bonow et al., 2008).

1.4.2.2 Chronic AR

Surgery recommendations depend on the presence of symptoms, LVF and LV dimensions. Surgery is indicated in symptomatic patients with EF less than or equal 50%, it is also indicated in asymptomatic patients with LVEDD approaching 75 mm or with LVESD approaching 55 mm. Surgery is not indicated in asymptomatic patients, even in presence of severe AR, if these patients have normal LVF and normal LV dimensions (Bonow et al., 2008). In asymptomatic patients with normal LVF the progression to symptoms or LV dysfunction is about 4.5% per year and the mortality rate is 0.2% per year (Bonow et al., 2008). Medical treatment with vasodilators is indicated in symptomatic patients or patients having LV dysfunction and they are poor candidate for surgery (American College of et al., 2006; Bonow et al., 2008).

1.5 Surgery of the Aortic Valve

1.5.1 History of Aortic Valve diseases Therapy

In 1931, Paul Dudley White stated, "There is no treatment of aortic valve stenosis" (Lawrence H. Cohn, 2012). Medical therapy of aortic stenosis has not significant advanced (Carabello, 2002). On the other hand patients may tolerate aortic regurgitation for many years, but as the left ventricle starts to dilate, a progressive downhill course begins and early operation is warranted (Tornos et al., 2006). Definitive therapy of aortic valve diseases was unavailable till the advent of the CPB.

1.5.2 Cardiopulmonary Bypass (CPB)

On May 6, 1953 Gibbon performed his first successful operation using an extracorporeal circuit in a young woman who had a large atrial septum defect with a large left-to-right shunt (Gibbon, 1954). One year later, Lillehei and colleagues had introduced another intact subject as the ‘‘bubble

oxygenator'', opening the doors for open-heart surgery around the world (Warden, Cohen, Read, & Lillehei, 1954). CPB is the main safe way of providing adequate systemic perfusion during open-heart surgery as it provides oxygenated blood flow to the whole body organs when the heart and the lungs are not functional. Cardiopulmonary bypass is essential in all valvular operations and cannulation sites depend on the type and approach of valvular surgery (Nicolini et al., 2003).

1.5.3 Current Approaches for Aortic Valve Surgery

1.5.3.1 Conventional (Full Sternotomy) Aortic Valve Surgery (CAVR)

It is considered as the standard approach in aortic valve surgery (Kaiser et al.). A skin incision is performed from just below the suprasternal notch upwards extending downwards to the tip of the xiphoid process; the whole sternum is divided vertically with a blade saw. With this approach, cannulation sites for CPB would be the right atrial appendage for the venous cannula and the ascending aorta for the arterial cannula (Kaiser et al.). (Figure 1.7)

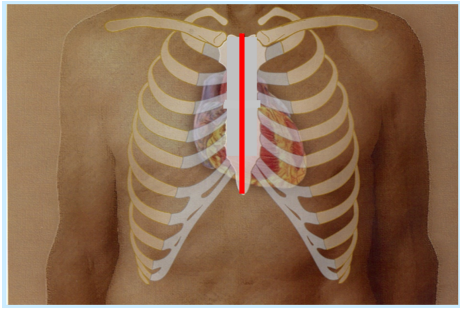

Figure 1. 7. Diagram showing the incision site for full sternotomy approach
(Source: Author collection from German Heart Center, Munich, Germany)

1.5.3.2 Minimally Invasive Aortic Valve Surgeries (MIAVR)

A-Upper Partial Sternotomy (J-shaped Hemisternotomy) approach: It is considered the most common approach in MIAVR nowadays (L. H. Cohn et al., 1997; Cosgrove & Sabik, 1996). Skin incision would be 6-8 cm in the midline over the upper part of the sternum extending from the suprasternal notch up to the 3rd or 4th intercostal space. The sternum is divided with a vertical blade saw, then the right half of the sternum is transected in the third or fourth intercostal space (J-shaped sternotomy) (Svensson & D'Agostino, 1998). With this approach, cannulation for CPB is usually intra-thoracic, with the aortic cannula in the ascending aorta and the venous cannula in the right atrium, or less commonly, a percutaneous long venous cannula is placed via the right or the left femoral veins into the right atrium (Svensson & D'Agostino, 1998). (Figure 1.8)

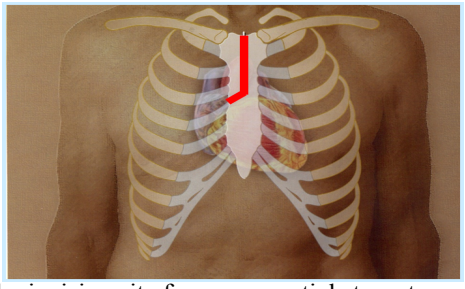

Figure 1. 8. Diagram showing the incision site for upper partial sternotomy approach
(Source: Author collection from German Heart Center, Munich, Germany)

B- Right Anterolateral Thoracotomy approach: It is performed through an incision over the second intercostal space at the right sternal edge. Arterial and venous cannulation is performed peripherally (more common) or centrally (less common). Special aortic cross clamps and instruments may be required to facilitate this procedure. The rest of the operation is the same as for any other minimal access aortic valve surgery. Since the anatomical relationships of the aorta and aortic valve are important for a successful operation, they emphasize the need of careful evaluation of the preoperative multi-slice computed tomography for surgical planning (Glauber et al., 2013). Some groups consider this approach the access of choice for MIAVR. On the other hand, this approach may be undesirable in females due to the position of the scar. (Figure 1.9)

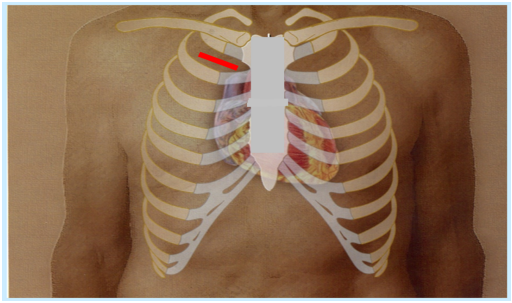

Figure 1. 9. Diagram showing the incision site for right anterolateral thoracotomy approach
(Source: Author collection from German Heart Center, Munich, Germany)

C- Right Parasternal approach*:* In 1998, Cohn and Minale et al described their experiences with this approach for AVR. It was performed via a vertical upper right parasternal incision where the second, third and fourth costal cartilages had to be removed and the right mammary artery (RIMA) usually sacrificed. The arterial and venous cannulation was performed centrally or peripherally. At that time, they recommended this approach for MIAVR due to its low mortality and morbidity rates (L. H. Cohn, 1998; Minale, Reifschneider, Schmitz, & Uckmann, 1998). At present, this technique has been abandoned due to its associated disadvantages (scarification of the RIMA, removal of 3 costal cartilages may cause lung herniation and the higher postoperative pain). Nevertheless, it is still very helpful in particular cases (Mazzitelli, Bedda, Petrova, & Lange, 2004) (Figure 1.10).

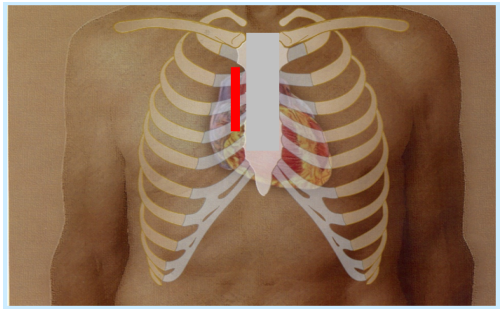

Figure 1. 10. Diagram showing the incision site for right parasternal approach
(Source: Author collection from German Heart Center, Munich, Germany).

D- Transverse Sternotomy approach: Cosgrove and colleagues introduced this approach in 1997 (Bridgewater, Steyn, Ray, & Hooper, 1998). It was performed via 8-10 cm transverse incision at the level of the manubrio-sternal angle extending in both sides. The mammary vessels on both sides were sacrificed. A transverse sternotomy is performed across the sternal angle. Arterial cannulation was central and venous cannulation was peripheral (Bridgewater et al., 1998). The rest of the operation was performed as usual. As the mammary vessels should be bilaterally sacrificed, precluding the possibility of future CABG procedures, and because of the high incidence of sternal dehiscence observed, this approach has been abandoned as well (Figure 1.11).

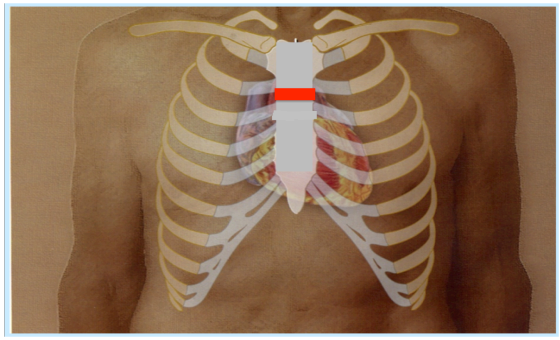

Figure 1. 11. Diagram showing the incision site for transverse sternotomy approach
(Source: Author collection from German Heart Center, Munich, Germany).

1.5.4 Percutaneous Valvular Interventions

1.5.4.1 Percutaneous Aortic Balloon Valvotomy

A percutaneous balloon is inserted and introduced through the aortic valve under fluoroscopy control via the femoral artery. During balloon inflation within the valve orifice fracturing the calcified areas dilates the narrow valvular cusps and opening of the fused commissures is achieved (Safian et al., 1988). Balloon valvotomy is rarely successful in case of severe calcifications as it has a high risk of stroke due to detached calcific emboli and may result in a significant

postoperative AR. In addition to that, the long-term outcomes of this procedure in adults are disappointing since restenosis is frequently observed in the first year. For all those reasons, it cannot be considered as true alternative therapy in case of AS, but only as a palliative procedure (Bernard et al., 1992; "Percutaneous balloon aortic valvuloplasty. Acute and 30-day follow-up results in 674 patients from the NHLBI Balloon Valvuloplasty Registry," 1991).

1.5.4.2 Transcatheter Aortic Valve Implantation (TAVI)

Recently, new techniques have been developed to implant prosthetic valves interventionally through transfemoral or transapical catheter-based approaches. Although surgical aortic valve replacement is the definitive treatment of AS, up to one third of patients are not candidates for surgery due to increasing age, heart failure or other comorbidities (Zajarias & Cribier, 2009). The history of percutaneous treatment of aortic valve disease with different types of devices goes back to the Danish researcher, H.R. Andersen, who in late 1980s experimented a balloon-expendable stented valve in an animal lab (a pig) (Andersen, Knudsen, & Hasenkam, 1992). The first clinical application of human transcatheter valve implantation took place in 2002 (Cribier et al., 2002).

In this procedure a new aortic valve is implanted in the same place of the original valve and the old valve is not excised, as what happens in surgical AVR. The new valve will press the original valve against the wall of the aorta allowing the new valve to take the place and the function of the native valve. This procedure doesn't need CPB. The valve may be implanted through different accesses, most commonly transfemorally via the right or the left femoral vessels (Figure 1.12), or transapically through a left lateral mini-thoracotomy incision (Figure 1.13). In the past few years new access points have been used including the subclavian and carotid arteries and direct implantation through the ascending aorta via a small right mini-thoracotomy incision. The new valve is implanted under fluoroscopic and echocardiographic guidance (Lawrence H. Cohn, 2012).

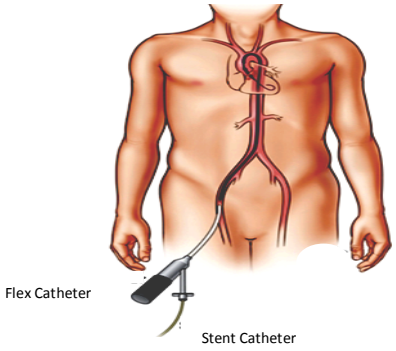

Figure 1. 12. Diagram showing transfemoral valve implantation
(Source: Cohn LH: Cardiac Surgery in the Adult, 4th Edition (Lawrence H. Cohn, 2012)).

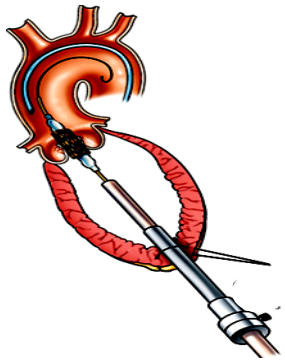

Figure 1. 13. Diagram showing transapical valve implantation
(Source: Cohn LH: Cardiac Surgery in the Adult, 4th Edition (Lawrence H. Cohn, 2012)).

1.6 Types of Prostheses used for Aortic Valve Replacement

The first surgical aortic valve replacement was done in 1952 by Hufnagel, who used an aortic valve ball and cage prosthesis implanted heterotopically in the descending thoracic aorta to treat a patients with aortic regurgitation (Hufnagel & Harvey, 1953) (Figure 1.14). After the advent CPB, initial attempts of AV replacement consisted of replacement of the individual aortic cusps with prosthetic ones sewn to the annulus. Unfortunately, even when successful, these prostheses usually calcified and the results were poor. Shortly after that, surgical pioneers (Starr, Braunwald and Harkin) began replacement of the AV in the orthotopic position (Lawrence H. Cohn, 2012).

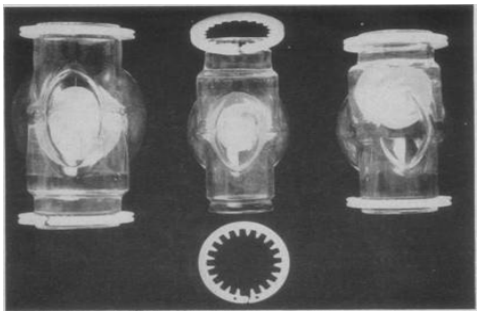

Figure 1. 14. Hufnagel valve
(Source: Canadian Medical Association Journal 1955 (Gravel, 1955))

1.6.1 Mechanical Prostheses

The ball and cage (Figure 1.15) is the first generation of aortic valve prostheses, which became the standard for AVR for more than a decade. Many of these valves have remained durable for up to 40 years (Gao, Wu, Grunkemeier, Furnary, & Starr, 2004). However, these valves needed intense anticoagulation (Ezekowitz, 2002). Innovators such as Björk, Hall, Kaster and Lillehei develop three models of tilting disc prostheses (Figure 1.16) which became the second generation of commonly implanted aortic valve replacement devices between 1968 and 1980 (Lawrence H. Cohn, 2012). Gott and Daggett developed the first bileaflet valve in 1963, which was followed by

Kalke and Lillehei first rigid bileaflet valve in 1976. Due to the high incidence of thromboembolic events, these valves had a limited use. In 1977 the St. Jude Medical (SJM) (Figure 1.17) prosthesis was developed and implanted by Nicoloff and colleagues (Emery et al., 1979): this is considered as the third generation of mechanical valves.

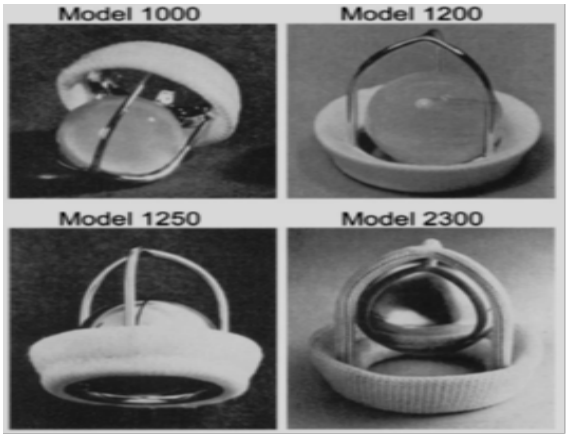

Figure 1. 15. Models of the ball and cage valve
(Source: Annals of Thoracic Surgery 2003 (Gott, Alejo, & Cameron, 2003))

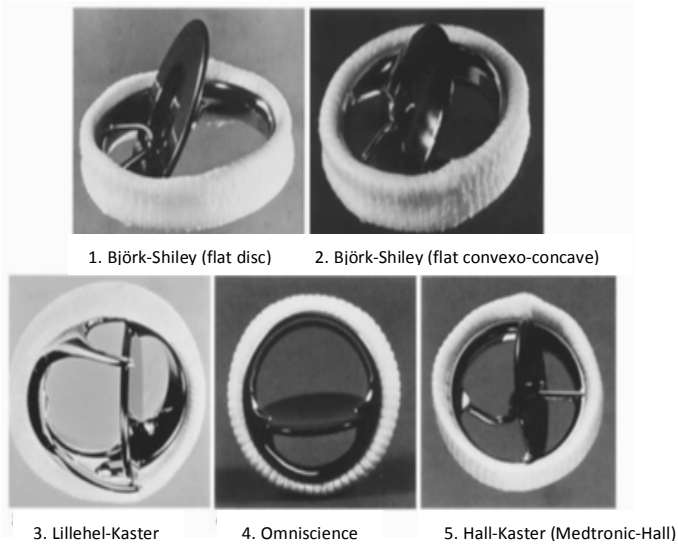

Figure 1. 16. 2nd generation mechanical prostheses
(Source: Annals of Thoracic Surgery 2003 (Gott et al., 2003))

Over the following decades bileaflet valves have been implanted extensively. The SJM prostheses demonstrated excellent hemodynamics with low gradients, minimal aortic insufficiency and low rates of thromboembolic events (Emery et al., 1979). Additionally, the need for anticoagulation with these valves was lower than with previous models (Emery et al., 2008). After introduction of the SJM valve, many other third generation models of bileaflet prostheses were developed, including the Sulzer Carbomedics valve (Sorin S.p.A., Milan, Italy), ATS medical prosthesis (Medtronic, Minneapolis, MN), and the On-X prosthesis (On-X Life Technologies, Inc., Austin, TX) (Figure 1.17).

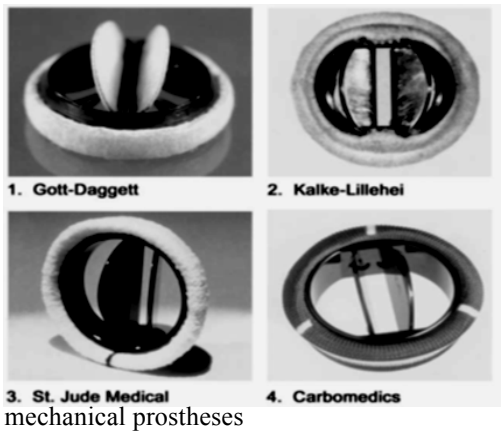

Figure 1. 17. 3rd generation mechanical prostheses
(Source: Annals of Thoracic Surgery 2003 (Gott et al., 2003))

The main advantage of mechanical prostheses is the long life span. Since there is no structural degeneration, they are at low-risk for re-operation. These may be needed only in cases of infection, prosthesis dysfunction caused by thromboembolism at the prosthesis leaflet or at the surrounding tissue. These events are usually avoided with adequate anticoagulation therapy (Hammermeister et al., 2000; Lund, Nielsen, Arildsen, Ilkjaer, & Pilegaard, 2000). The main disadvantage of these valves is the high risk of bleeding complications due to the lifelong need for oral anticoagulation, e.g. the risk of intracranial bleeding increases with age due to aging process of the vessels which becomes more fragile and more vulnerable for rupture in case of systemic hypertension (Hirsh, Dalen, Guyatt, & American College of Chest, 2001; Minakata et al., 2002).

Due to their advantages and the disadvantages, guidelines have been published, which indicate which type of prosthesis should be used in which group of patients. The ACC/AHA guidelines in 2006 for the management of patients with valvular heart disease recommend the implant of a mechanical prostheses in patients younger than 65 years old as the risk reoperation because of the degeneration of the biological prostheses are more than the risk of bleeding due to oral anticoagulation therapy (American College of et al., 2006).

1.6.2 Biological Prostheses (Bioprostheses)

The main advantage of the biological prostheses is the lack of need for long time oral anticoagulation; hence, there is a much lower risk of bleeding especially in elderly. On the other hand, these valves are always exposed to degenerative process and there is a higher risk of re-operation, which increases over time, this risk is in higher rates in younger patients. Degenerative changes are inversely proportional to the age of the patients (i.e. there is a decrease in the degenerative changes with increased age). The ACC/AHA guidelines in 2006 recommend the use of biological valves in patients older than 65 years old (American College of et al., 2006).

1.6.2.1 Stented Pericardial and Porcine Bioprostheses

They are usually made of porcine aortic valves or bovine pericardium (Figure 1.19). Over the past 40 years, advances in tissue fixation methodology and chemical treatments have been developed to prevent calcium deposition. All porcine and bovine valves are preserved with glutaraldehyde, which acts by cross-linking collagen fibers to reduce tissue antigenicity. Glutaraldehyde also ameliorates in vivo enzymatic degradation and causes the loss of cell viability, thereby preventing extracellular matrix turnover (Hilbert & Ferrans, 1992). Glutaraldehyde fixation in case of porcine valves can be performed at high pressure (60 to 80mmHg), low pressure (0.1 to 2 mmHg), or zero pressure (0mmHg) where it retains the collagen architecture of the relaxed aortic valve cusp (Flomenbaum & Schoen, 1993). Pericardial prostheses are fixed in low or-zero pressure conditions.

I- Heterograft (Xenograft):

First-Generation: They were preserved with high-pressure fixation and were placed in annular position. They include the Medtronic Hancock standard and Modified orifice (Medtronic, Minneapolis, MN), and Carpentier-Edwards Standard porcine prostheses (Edwards Life Sciences, Irvine, CA) (Lawrence H. Cohn, 2012).

Second-Generation: They are preserved with low or-zero pressure fixation. Some of these valves may be also placed in the supraannular position, which allows placement of a slightly larger prosthesis. They include Medtronic Hancock II valve (Medtronic), Medtronic Intact porcine valve (Medtronic), and Carpentier-Edwards supraannular valve (SAV) (Edwards Life Sciences). Pericardial prostheses include the Carpentier-Edwards Perimount (Edwards Life Sciences) and the Pericarbon prostheses (Sorin Biomedica, Saluggia, Italy) (Lawrence H. Cohn, 2012).

Third-Generation: This generation incorporates zero- or low-pressure fixation with antimineralization process that are designed to reduce material fatigue and calcification. Stents become thinner, a lower profile, more flexible, and the sewing ring become scalloped for supra-annular placement. They include the Medtronic Mosaic porcine valve (Medtronic), the St. Jude Medical Epic valve (St. Jude Medical, Inc.) which is a porcine valve, the Carpentier-Edwards Perimount Magna valve (Edwards Life Science) which is a pericardial valve and the Mitroflow Pericardial aortic prosthesis (Carbomedics) pericardial valve (Lawrence H. Cohn, 2012).

II- Transcatheter bioprostheses:

Transcatheter heart valves are now a clinical reality for high-risk patients. (Webb et al., 2007). The two most implanted valve systems are the Edwards Sapien valve and the Corevalve, although many other valves exist now in different stages of development and evaluation. Each valve system includes valve prosthesis, a stent or frame, a loading system and a delivery system. The Edwards Sapien (THV) valve (Edwards Life Science Inc., Irvine, CA) is composed of a bovine pericardial valve on a balloon-expandable stent, whereas the Corevalve (Medtronic) is a porcine pericardial valve on a self-expanding nitinol frame (Lawrence H. Cohn, 2012). (Figure 1.18)

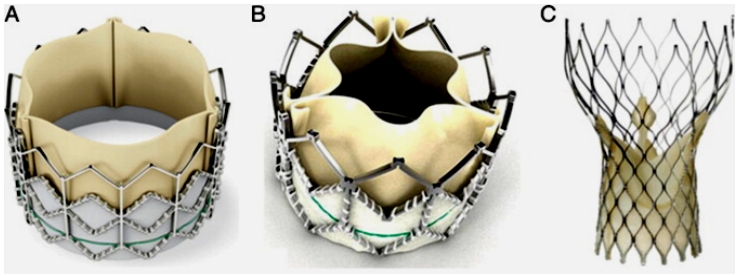

Figure 1. 18. Current widely available Transcatheter bioprostheses
(A) The Edwards Sapien THV balloon-expandable valve (Edwards Life sciences, Irvine, California) (B) The Sapien XT THV (Edwards Life sciences) (C) The Medtronic Corevalve (Medtronic, Minneapolis, Minnesota).
(Source: J Am Coll Cardiol. 2012; 60 (6): 483-492.doi: 10.1016/j.jacc.2012.01.071 (Webb & Wood, 2012))

1.6.2.2 Stentless Bioprostheses

Many clinical reports have shown excellent results up to 20 years with pericardial and porcine stented prostheses (Yankah, Schubel, Buz, Siniawski, & Hetzer, 2005) (Figure 1.19). However, all these valves are mounted on a stent and have a ring, usually covered with a Dacron cuff for suturing. In cases of a small and calcified annulus significant residual gradient may be observed after the implantation. Stentless bioprostheses have been designed in order to overcome some of the disadvantages of the stented valves (David et al., 1994) (Figure 1.19). However, they are more difficult to insert, associated with increased cross-clamp time, and their intermediate results do not translate in improved long-term results (Cohen et al., 2010). In addition, some of these valves showed higher rates of structural failure in comparisons with stented valves, due to wearing and tearing at the commissures (David, Feindel, Bos, Ivanov, & Armstrong, 2008), most common types of stentless bioprostheses are:

I-Homograft: The first choice of aortic valve replacement was the homograft aortic valve. Gordon Murray created an animal model to implant an aortic homograft valve in the descending aorta

(Murray, 1956) and was the first to apply the concept in the human demonstrating function for up to 4 years (Murray, 1960). Duran and Gunning at Oxford described a method for orthotopic (subcoronary) implantation of such valves in 1962 (Duran & Gunning, 1962). In the same year Donald Ross in London and Sir Brian Barratt-Boyes in Auckland did this successfully in humans (Barratt-Boyes, 1964; D. N. Ross, 1962).

Homograft valves can be obtained from donors whose beating hearts are not suitable for heart transplantation but the larger source of homograft valves are from non-beating heart donors. There are many problems in cases of the use of homograft valves in AVR, such as body rejection of the transplanted valve, which require the use of immunosuppression to avoid that. Also the matching problem between the available homograft and the recipient patient, the implanted homograft would undergo degeneration and annulus-dilatation with time (Jones, Hance, Stelzer, & Elkins, 1988).

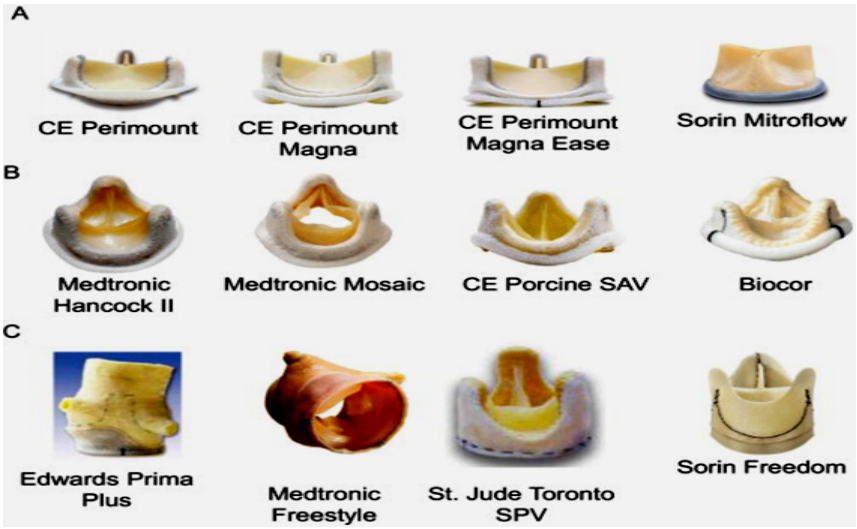

Figure 1. 19. Types of Stented and Stentless bioprostheses

(A) Stented pericardial bovine bioprostheses. (B) Stented porcine bioprostheses. (C) Stentless bioprostheses. These lists are non -exhaustive. CE = Carpentier-Edwards; SPV = Stentless porcine valve.

(Source: J Am Coll Cardiol Intv. 2011; 4(7): 721-732. doi: 10.1016/j.jcin.2011.03.016 (Piazza et al., 2011))

II-Autograft: Experimental use of autologous valve transplantation began in 1960 when Lower and colleagues at Stanford transposed the autologous pulmonary valve to the mitral position in dogs (Lower, Stofer, & Shumway, 1961). Shortly after that to the aortic position (Pillsbury & Shumway, 1966). Donald Ross applied this to humans, reporting in 1967 his clinical experience replacing either the aortic or mitral valve with a pulmonary autograft (D. N. Ross, 1967). Later on, the use of autograft valves took place in America by Elkins and Stelzer (Stelzer & Elkins, 1987).

This operation is known as the Ross procedure. After an initial surge of interest in the 1990s (more than 240 surgeons worldwide reported their experience to the Ross procedure International

Registry (Oury, Hiro, Maxwell, Lamberti, & Duran, 1998). Its use was diminished in the subsequent decade (Lawrence H. Cohn, 2012). On the other hand the use of autograft valves had shown an excellent results due to the longer life span even in younger patients (patients under 50 years old in which a heterograft implantation has faster degenerative changes), there is no need for the use of oral anticoagulation and there is a reduced risk for valve endocarditis (J. W. Brown et al., 2006; Takkenberg et al., 2009).

1.6.2.3 Sutureless Bioprostheses

Recently, sutureless bioprostheses (Figure 1.20) have been introduced in order to obtain the hemodynamic benefits of stentless valves without the increased difficulty in surgical implantation. The design of these prostheses intends to be an alternative to the traditional prostheses (stented or stentless) used in conventional open-heart surgery (Folliguet et al., 2012). For implantation of these valves, only 1 to 3 sutures are needed, compared to the 12-15 sutures needed for conventional valves. Therefore, the most important advantage of the sutureless valves is the reduction of the cross clamp-time and the easy of implantation. Potentially, the limited number of the needed stitches could also reduce the risk of aortic annulus tearing and the risk of injury of the bundle of His. Due to the relative ease of implantation, it has also been advocated, that these valves could favor the expansion of minimally invasive approaches (Shrestha et al., 2009).

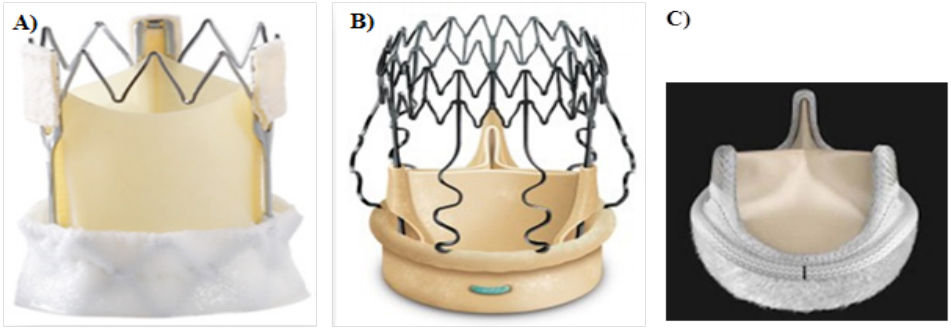

Figure 1. 20. Sutureless bioprostheses

(A) The 3f Enable aortic bioprostheses (Medtronic, Minneapolis, MN) (Martens et al., 2011).

(B) The Perceval S sutureless biological valve (Sorin Group, Saluggia, Italy) (Folliguet et al., 2012).

(C) INTUITY Valve System (Edwards Life sciences Corporation, Irvine, CA) (Borger, Dohmen, Misfeld, & Mohr, 2013).

2. Background and Aims

Conventional aortic valve replacement (CAVR) through full sternotomy (FS) is the standard therapy of aortic valve diseases (American College of et al., 2006). The clinical outcomes after CAVR have improved dramatically in the past decade, despite the increase in the patients' age and overall risk factors (e.g. associate comorbidities). The most recent reported data from the society of thoracic surgeons showed an overall mortality rate of 2.6% and stroke rate of 1.4% following isolated AVR (J. M. Brown et al., 2009; Malaisrie et al., 2010).

The term "minimally invasive" refers to a smaller incision in the chest wall. Over the past two decades, minimally invasive cardiac surgery techniques have been increasingly adopted with the goal to reduce the invasiveness of the surgical procedure and aiming in the same time to offer the same quality, safety and results of standard conventional surgery. The main aim of the minimally invasive surgeries is that smaller incisions may reduce intraoperative trauma, bleeding and may also accelerate postoperative recovery and also reduce the procedure-related costs. In addition to that, smaller surgical scars and faster recovery increase patients' satisfaction. Since the mid-1990s, several minimally invasive approaches for aortic valve surgery (upper partial sternotomy, anterolateral minithoracotomy, right parasternal thoracotomy or transverse sternotomy) have been introduced and have been increasingly used.

The upper partial sternotomy approach in particular has been widely analyzed in the reported literature, showing some benefits in comparison to the conventional median sternotomy approach. In these reports, the most common advantages of this technique included decreased blood loss, less postoperative pain, decreased ventilation time, shorter ICU- and hospital stay and better cosmetic results (Bonacchi, Prifti, Giunti, Frati, & Sani, 2002; Doll et al., 2002; Tabata et al., 2008; von Segesser et al., 1999). In spite of that, randomized controlled trails as well as meta-analysis studies (Aris et al., 1999; J. M. Brown et al., 2009; Dogan et al., 2003; Murtuza et al., 2008) were not able to show a convincing superiority of MIAVR over CAVR.

We hereby aimed to assess retrospectively the efficacy of both approaches (MIAVR; via upper partial sternotomy and CAVR; via full sternotomy) and to test if MIAVR offers any superiority over CAVR procedure. Furthermore we developed a propensity score match to avoid influences of bias between the two groups in the preoperative baseline characteristics and associated comorbidities. Thus, a fair comparison was achieved between the two procedures.

3. Material and Methods

3.1 Study Design

After being approved by our institutional research board, a chart review was performed of patients' records and departmental database for all patients who underwent AVR either through conventional or minimal invasive approach. A total of 2103 Patients who underwent primary isolated AVR (CAVR, n=1167 and MIAVR, n=936) in the period from January 2001 until May 2012 at our department of cardiovascular surgery (in German Heart Center Munich) was included in the study. The study was carried out as a retrospective, observational, nonrandomized study of a single-center series. A follow up range up to 10 years was recorded for 98% of the patients.

3.2 Patient Selection

3.2.1 Inclusion Criteria

All patients with isolated aortic valve disease (stenosis, regurgitation or mixed pathology) who admitted to our department were included in the study. All underwent isolated AVR for the first time. Concomitant cardiac pathologies were present in some cases and were operated at same time during the AVR (e.g. supracoronary ascending aorta aneurysm which indicated repair and not replacement, left ventricular outflow obstructions (LVOTO) which indicated subvalvular myectomy).

3.2.2 Exclusion Criteria

Primary exclusion criteria from our database included: redo cardiac surgery (previous aortic valve replacement, coronary artery bypass grafting, mitral valve surgeries or tricuspid valve surgeries), patients underwent aortic valve repair (e.g. David repair), patients underwent transcatheter aortic valve implantation (TAVI), AVR which initiated as TAVI and underwent an intraoperative conversion into conventional aortic valve surgery, patients underwent AVR associated with aortic root or aortic arch aneurysm surgeries (e.g. Bentall, Yacoub procedures), or supracoronary ascending aorta aneurysm which indicated replacement and could not be repaired, and patients underwent AVR concomitant with other cardiac procedures were also excluded from the study (e.g. other valvular diseases, coronary artery diseases (CAD), atrial septal defect (ASD), ventricular septal defect (VSD), patent foramen oval (PFO)...etc.).

3.3 Population Flowchart

Our study flowchart is illustrated in (Figure 3.1); where initial data collection from 2416 patients underwent AVR were evaluated and a final data of 2103 patients were used for statistical analysis after applying the inclusion and exclusion criteria. The study population was divided into the following 2 groups:

- Group1: MIAVR via upper partial sternotomy: 936 patients.
- Group 2: CAVR via full sternotomy: 1167 patients.

To exclude the effect of selection bias a propensity score matched analysis was applied for each of these 2 groups, a subgroup of patients without significant differences in their baseline characteristics were matched. That created a kind of fair comparison between both groups:

- Subgroup 1: Included 585 matched patients from the MIAVR group.
- Subgroup 2: Included 585 matched patients from the CAVR group.

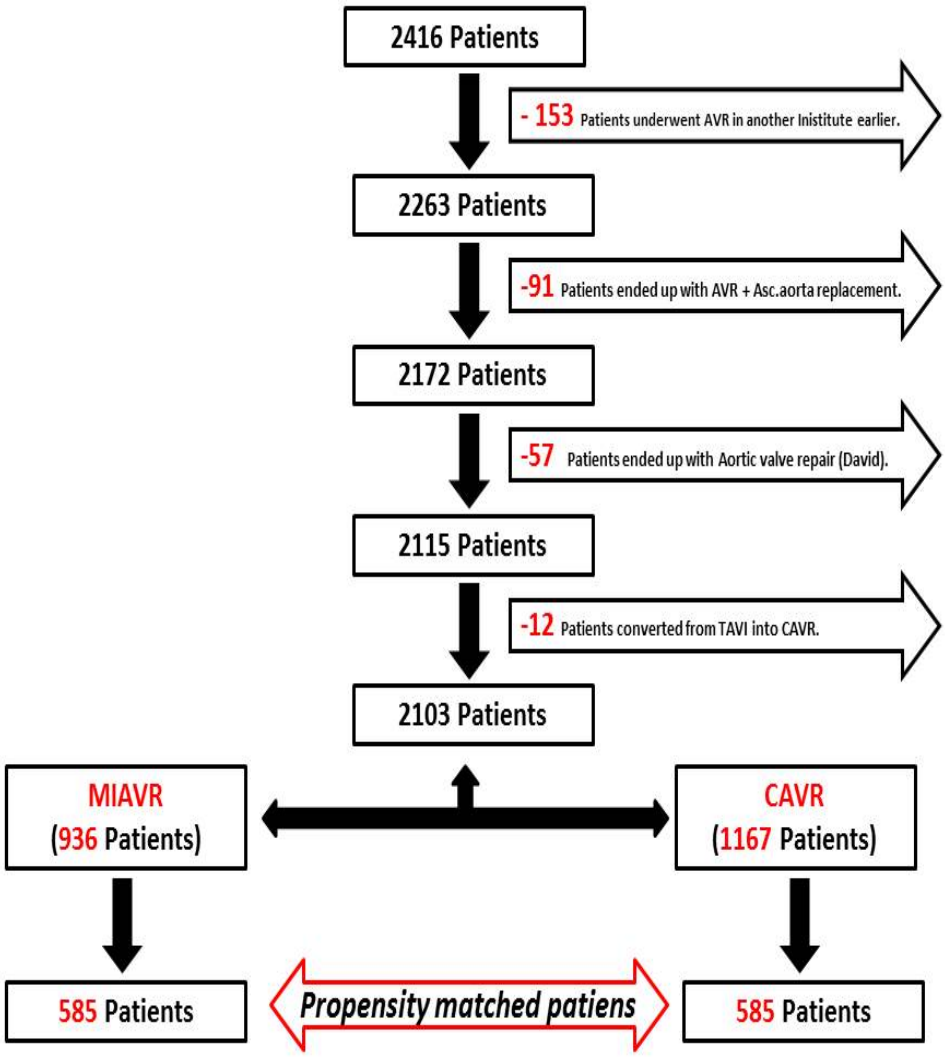

Figure 3. 1. Population flowchart

3.4 Preoperative Planning and Surgical Techniques

3.4.1 Patients preparation

The preoperative assessment of the patients included a clinical examination, laboratory examination and evaluation of cardiac risk factors. All patients underwent examination with electrocardiogram (ECG), chest x-ray, transthoracic echocardiography (TTE) (Figure 3.2), coronary angiography, pulmonary function tests and carotid artery ultrasonography.

The echocardiographic protocol included measurements of the aortic annulus, the interventricular septum, the transaortic valve peak and mean gradient, aortic valve area and the left ventricular ejection fraction using commercially available ultrasound systems (Siemens, ACUSON. Sequoia. 512. Erlangen. Germany). Left ventricular ejection fraction (LVEF) was estimated according to Simpson's rule. The simplified Bernoulli equation was used to calculate the transaortic gradients and the aortic valve area (AVA) was calculated by the continuity equation. Experienced echocardiographers performed all echocardiographic examinations. TEE is more accurate way to measure the AVA and gives more information about the morphological changes in the aortic valve (Blumberg et al., 1997). It has more diagnostic importance with patients whose body habits do not allow proper assessment with the transthoracic echocardiography. (Figure 3.3)

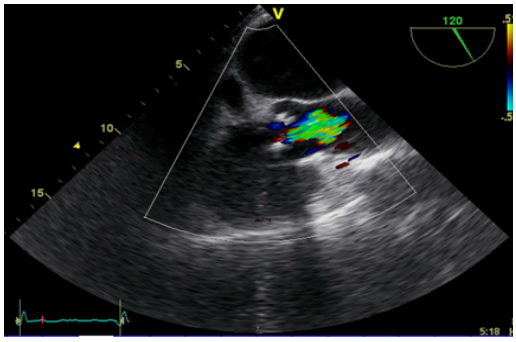

Figure 3. 2. TTE showing AS

(Source: Author collection from German Heart Center, Munich, Germany).

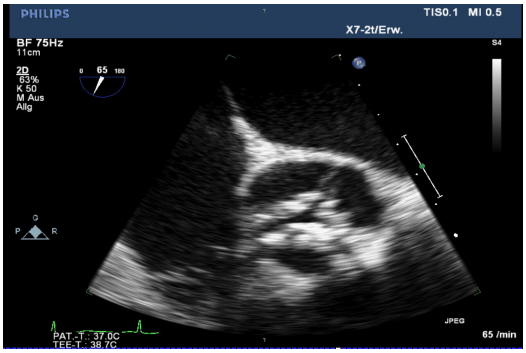

Figure 3. 3. TEE showing AS

(Source: Author collection from German Heart Center, Munich, Germany).

3.4.2 Anesthesia

Fasting for at least 6 hours before each cardiac surgery procedure is a mandatory in our institute, patients usually received Tranxilium 10-20 mg PO (Dikaliumclorazepat, Sanofi Aventis GmbH, Frankfurt am Main, Germany) at the night before the surgery, and a premedication of Rohypnol 1-2 mg PO (Flunitrazepam, Hoffmann-La Roche AG, Basel, Switzerland) in the early morning of the surgery day

For induction of anesthesia patients usually received intravenous Dormicum (Midazolam, Hoffmann-La Roche AG, Basel, Switzerland), Sufentanyl 0.5-1µg/kg (Fentanyl-Janssen, Janssen-Cilag GmbH, Neuss, Germany) and intravenous Rocuronium 0.5-1mg/kg (Esmeron, MSD Sharp & Dohme GmbH, Haar, Germany) for relaxation.

For maintenance of anesthesia patients usually received a combination of inhalation anesthesia of Sevorane 1-2% (Sevofluran, Abbott GmbH & Co KG, Wiesbaden, Germany) and intravenous Propofol 3-5 mg/kg/h. (B.Braun Melsungen AG, Melsungen, Germany) and Sufentanyl 0.5-1µg/kg/h. (Fentanyl-Janssen, Janssen-Cilag GmbH, Neuss, Germany), and bolus doses of Rocuronium 0.5mg/kg (Esmeron, MSD Sharp & Dohme GmbH, Haar, Germany) as indicated.

After endotracheal intubation the patient would mechanically ventilated with volume controlled modality (Dräger Kato Mechanical Ventilator, Dräger Medical Germany GmbH, Lübeck, Germany) then each patient would get a Nasogastric (NG) tube and transurethral urinary catheter with a probe for body temperature and urine output monitoring during the procedure. Central venous catheter (CVC) (Certofix B, B.Braun Melsungen AG, Melsungen, Germany) was also placed into the right Internal Jugular vein with Seldinger-Technique. An arterial catheter would be placed into the radial or femoral arteries for a continuous assessment of the blood pressure and allows a regular examination for the arterial blood gases (ABGs).

Continuous clinical monitoring during the operative procedure included seven leads electrocardiography, invasive arterial blood pressure, central venous pressure, pulmonary artery pressure, urine output, temperature, and pulse oximetry, capnography, bispectral index (BIS). Intra-operative TEE was routinely used in all procedures for assessment of the cardiac function, evaluation of the surgical result and confirmation of the de-airing process (especially in MIAVR as the difficulty of air removal from the heart at the end of surgery is one of the major concerns about MIAVR procedures (Cooley, 1998; Vanoverbeke et al., 2004)).

3.4.3 Surgical Techniques

The decision whether patients received a minimally invasive or a conventional procedure was based on the evaluation of general patient status, associated comorbidities, and anatomical consideration. This decision was taken in the contest of a preoperative meeting.

3.4.3.1 Conventional aortic valve replacement (CAVR)

The routine skin incision was performed along the sternum starting from the suprasternal notch extending to the lower edge of the xiphoid process. A standard vertical full sternotomy was performed with a blade saw. Then, the mediastinum was exposed with a standard chest retractor. A T-shaped pericardiotomy was performed and traction sutures were placed to suspend the pericardium and to expose the heart.

Cannulation of the CPB was achieved after full systemic heparinization (Figure 3.4). The arterial cannula was usually placed into the ascending aorta, and the venous cannula through the right atrial appendage into the right atrium. After initiation of CPB, the distal aorta was cross-clamped and myocardial protection was obtained with moderate systemic hypothermia at 32°C and cold crystalloid cardioplegia. Cardioplegia solution was administrated antegradely via the aortic root cannula or through direct coronary cannulation in case of aortic regurgitation. If needed, maintenance of cardiac arrest thereafter was achieved by direct administration of cardioplegia into the coronary ostia. A left ventricular vent was placed through the right superior pulmonary vein.

After aortotomy, three traction sutures at the tip of each commissure were placed and suspended to the drapes for better exposure of the aortic valve. The diseased valve was excised and the annulus was carefully decalcified. An adequate-sized prosthesis was implanted and fixed with pledged U-sutures. After closure of the aortotomy and de-airing of the heart, the aorta was de-clamped and the patient weaned from CPB. TEE was always used to confirm the function of the new valve. One or two chest tubes were placed in the mediastinum, and the sternum was approximated with wires. The skin, subcutaneous, and muscle layers were closed layer by layer in standard fashion.

3.4.3.2 Minimally invasive aortic valve replacement (MIAVR)

A limited median 6-8 cm skin incision was made over the upper part of the sternum (Figure 3.5). An upper partial sternotomy is performed using an oscillating saw down to the third or fourth

intercostal space at which a transverse right sternal transection is performed (J-shape sternotomy). The upper part of the sternum was exposed with a small retractor. The upper part of the pericardium was incised and pericardial stay sutures were placed for better exposure of the aorta and right atrium.

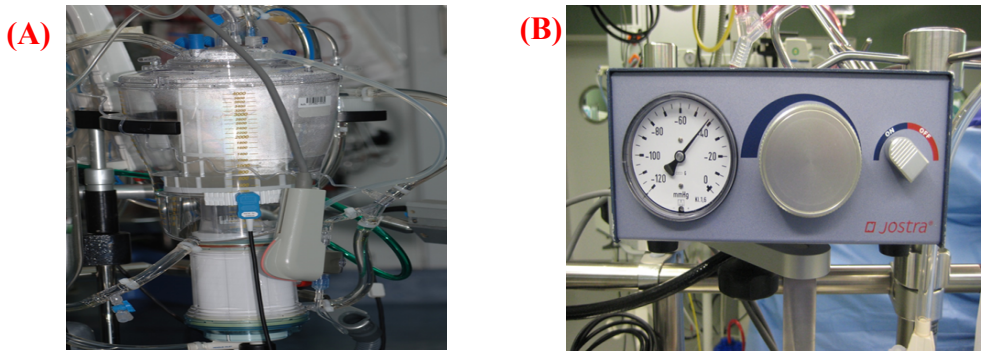

Figure 3. 4. (A) Primox (Dideco) oxygenator for CPB (B) Vacuum controller of CPB
(Source: Author collection from German Heart Center, Munich, Germany)

After full systemic heparinization, cannulation for CPB followed (Figure 3.4). Despite of the small-sized incision and the tight operative field, central (intrathoracic) cannulation was routinely performed in our institute. The arterial cannula was usually placed into the ascending aorta, whereas the venous cannula was commonly placed into the right atrial appendage. Less commonly a long venous cannula was placed through the femoral vein into the right atrium under TEE control. A left ventricular vent was placed through the right superior pulmonary vein. The operation would proceed in the same way as for CAVR described above.

After the procedure patients were admitted to the intensive care unit (ICU) where they weaned from the mechanical ventilator as soon as possible. Shortly after that, patients were mobilized with the help of physiotherapists. Later on, patients were discharged to the normal ward as soon as they became circulatory and respiratory stable, where they received psychosomatic therapy till discharge into the rehabilitation facility.

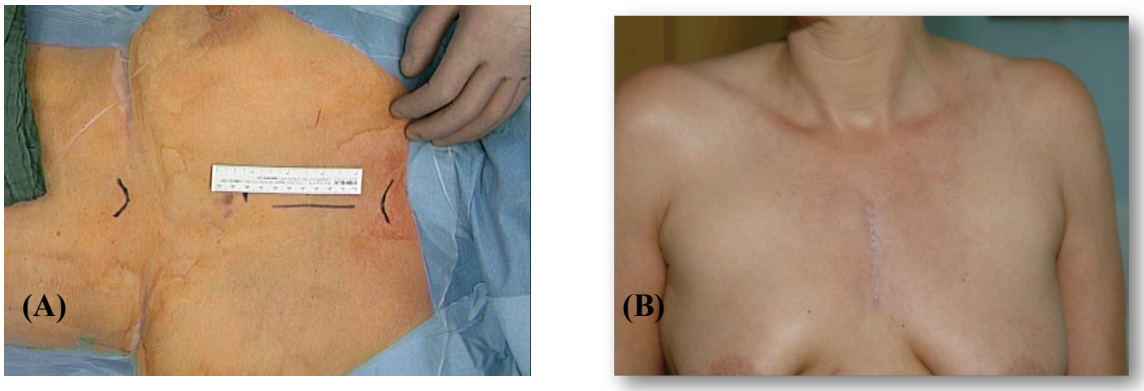

Figure 3. 5. (A) Site of incision for MIAVR (Intraoperative) (B) Shape of the wound after MIAVR
(Source: Author collection from German Heart Center, Munich, Germany)

3.5 Definition of Outcomes

3.5.1 Procedural Outcomes

Aortic cross clamp time is defined as the period of cardiac arrest. It starts from applying the aortic cross clamp onto the ascending aorta till de-clamping. Cardiopulmonary bypass time is the period of time from start to end of CPB; it includes both the cross-clamp and reperfusion time (time between de-clamping the aorta and the end of CPB). Procedural time is defined as the whole operation time from skin incision till skin closure.

Intraoperative Auto-transfusion is the amount of autologous blood transfused, which mainly included the Cell-Saver blood collected from the surgical field during surgery, or the autologous blood or -plasma units, which were donated from the patient himself before the surgery.

Cardiac Output (CO): Is the amount of blood the heart pumps through the circulatory system in a minute. It reflects the overall health of the heart. Low cardiac output (LCO) is defined as the decrease in the blood volume pumped per minute by each ventricle. It is assessed by measuring the cardiac ejection fraction (EF) using the echocardiography or by measuring the cardiac index (CI) directly through pulmonary artery catheter which known as Swan-Ganz catheter. Low cardiac output was managed with catecholamine therapy (conservatively) or applying an Intra-Aortic Balloon Pump (IABP).

Intraoperative rhythm disturbance is the incidence of any kind of arrhythmias including atrial fibrillation or flatter, sick sinus syndrome, ventricular arrhythmias, atrioventricular block.

3.5.2 Postoperative Outcomes

Blood loss (drainage volume) is the amount of blood collected by the chest drains till removal of those tubes. Re-exploration for bleeding was indicated in cases of severe bleeding after the primary surgery. Blood transfusion in the ICU included all blood products transfused to the patient till discharge from the ICU.

Postoperative rhythm disturbance included the incidence of new onset atrial fibrillation, sick sinus syndrome or any degrees of atrioventricular block during ICU-stay and was persisted till discharge to the normal ward.

Intubation time is the period of mechanical ventilation time; it is calculated in this study by the time starts from ICU-admission till extubation. ICU-stay is the period of residence in ICU, which starts immediately after surgery till discharge to the normal ward. Hospital stay is defined as the whole period of hospital residence from preoperative admission until discharge to the rehabilitation after surgery.

Sternum Re-fixation is the need for sternum rewiring after the initial surgical closure mainly caused by postoperative wound infection mainly (it reflects and represents the incidence of wound infection in our study) or rarely due to wire damage.

Postoperative respiratory insufficiency is the incidence of any respiratory complications after surgery, which might need non-invasive ventilation (NIV), re-intubation and mechanical ventilation or even tracheostomy. In cases of tracheostomy a programmed gradual weaning from mechanical ventilator was taken through.

Postoperative renal insufficiency (failure) is diagnosed by an increase of the serum creatinine level than 1.5 mg/dl. It is usually associated with decreased urine output (oliguria or anuria). It was treated conservatively or with hemodialysis/hemofiltration. Hemodialysis is the removal of certain elements from the blood by virtue of the difference in rates of their diffusion through a semipermeable membrane while being circulated outside the body; the process involves both diffusion and ultrafiltration (Klingele et al., 2013; Valdez et al., 2013). The blood samples for laboratory investigations were collected immediate- and 4 hours- postoperatively and every day in the morning during ICU-stay and before hospital discharge.

Postoperative myocardial infarction was primary diagnosed with pathologic ECG for new ischemic changes with elevated serum level of creatinine kinase myocardial band (CKMB), and was confirmed with pathologic coronary angiography during the hospital stay after surgery.

Postoperative cerebrovascular accident was diagnosed if evidence was found of a new neurologic deficit with morphologic substrate confirmed by computed tomography or nuclear magnetic resonance imaging.

Re-AVR is the need for redoes surgery during hospital stay or early after discharge. Etiology of Re-AVR was mainly postoperative endocarditis, diagnosed according to Modified Duke's Criteria (Habib et al., 2009), paravalvular leakage for any reason (e.g. thrombosis on the nearby aortic

tissues) or valve degeneration (mainly in cases of biological prosthesis), the last two causes were usually diagnosed with echocardiography during follow up.

The 30-day mortality is defined as in hospital death or shortly after discharge within the first month after surgery. 1-year mortality is the death occurring within the first 12 months after surgery. Overall Mortality is the death caused by cardiac or non-cardiac reasons. About 2% of patients in each group were lost in follow up. So follow up was 98% completed.

3.6 Statistical Analysis

To reduce the effect of selection bias and potential confounding, the differences in the baseline characteristics were adjusted by developing a propensity score matching. Propensity score analysis is a simple method for reducing bias in retrospective observation- al studies. To estimate the propensity score for a particular patient in the MIAVR group, a logistic regression model was used. Eight variables were involved in logistic regression model to generate the propensity score (Appendix, Table 8.1): age, sex (female), weight, height, preoperative serum creatinine level, previous myocardial infarction, LV-EF and aortic valve pathology (isolated aortic stenosis). For the development of the propensity score-matched pairs, a 5–1 digit matching was used to identify the matched patients using the statistically software R (version 2.13.1). To calculate the probability for the matched patients with the 5–1 digit matching, the first stage would focus on matching those pairs that have exactly the first five decimal digits of their propensity score. For those that had not been matched yet, matching would continue by focusing on the first 4 decimal digits, then on first 3, first 2 and finally on first decimal digit of their propensity score (Parson, 2001).

The SPSS software, version 15.0 (Chicago, IL, USA) was used for data analysis. Continuous data were expressed as the mean± standard deviation (SD) or medians with interquartile ranges (IQRs), and categorical data were expressed as percentages or frequencies. The Kolmogorov–Smirnov test was used to check for the normality of distribution of the data in the two groups of patients before additional analysis. Differences between the two groups were compared with the use of a χ^2 test or Fisher's exact test (if the expected cell frequencies were <5) for categorical variables and the t-test or Wilcoxon rank-sum test for the continuous variables. Finally, Kaplan–Meier curves were used to estimate the survival functions for patients in both groups. Testing the difference between the survival curves was done with the use of the log-rank test. All reported P-values are two-sided and a value of $\boldsymbol{P < 0.05}$ was considered statistically significant.

4. Results

4.1 Results before Propensity Score Match (All patients)

4.1.1 Baseline (Demographic) Characteristics

The demographics characteristics for all patients are summarized in (Table 4.1). CAVR group were significantly older than MIAVR group. There were significant differences between both groups in regard to sex of the patients, the presence of diabetes mellitus, peripheral vascular diseases, chronic pulmonary diseases, preoperative renal insufficiency, cerebrovascular accidents, and the surgical indication.

Table 4. 1. Demographic characteristics for all patients

	MIAVR	**CAVR**	***P*-value**
All patients	**936**	**1167**	
Age (years), mean ± SD	62.8 ± 12.3	70.9 ± 11.7	**<0.001**
Female, n (%)	322 (34.4)	547 (46.9)	**<0.001**
Body mass index (Kg/m²), mean ± SD	27.3 ± 6.7	27.2 ± 4.8	0.9
Diabetes mellitus, n (%)	118 (12.6)	206 (17.7)	**0.009**
Systemic hypertension, n (%)	629 (67.2)	822 (70.4)	0.1
Peripheral vascular disease, n (%)	13 (1.4)	38 (3.3)	**0.006**
Previous peripheral vascular bypass, n (%)	21 (2.2)	27 (2.3)	0.92
Previous myocardial infarction, n (%)	21 (2.2)	28 (2.4)	0.82
Previous PTCA/Stent implantation, n (%)	38 (4.1)	54 (4.6)	0.47
Preoperative pacemaker, n (%)	20 (2.1)	46 (3.9)	**0.04**
Chronic pulmonary diseases*, n (%)	77 (8.2)	152 (13)	**0.003**
Previous cerebrovascular accident, n (%)	18 (1.9)	45 (3.9)	**0.02**
Creatinine (mg/dl), mean ± SD	1.0 ± 0.4	1.1 ± 0.5	**<0.001**
Renal insufficiency (Creatinine ≥ 1.5mg/dl), n (%)	37 (4.0)	114 (9.8)	**<0.001**
CK value (U/l), median (IQR)	78(48.3-117.8)	39 (24-74)	**0.06**
CKMB value (U/l), median (IQR)	6.5 (6-7.8)	8 (6-12.8)	0.18
Hemoglobin level (g/dl), mean ± SD	13.7 ± 1.4	13.1 ± 1.7	**<0.001**
Surgical indication			
Elective, n (%)	888 (94.9)	1030 (88.3)	**<0.001**
Urgent, n (%)	48 (5.1)	137 (11.7)	**<0.001**

Chronic pulmonary diseases* included chronic obstructive and restrictive pulmonary diseases.

4.1.2 Echocardiographic Data

The echocardiographic data for all patients are summarized in (Table 4.2). Patients in the CAVR group were more likely to have a lower ejection fraction, less cardiac index, and they had larger LVEDD than patients in the MIAVR group. There were no significant differences in regard to the underlying aortic valve pathology.

Table 4. 2. Echocardiographic data for all patients

	MIAVR	**CAVR**	***P*-value**
All patients	**936**	**1167**	
LV-Function			
EF* <35 %, n (%)	28 (3.0)	65 (5.6)	**0.003**
EF 35-50 %, n (%)	71 (7.6)	135 (11.6)	**0.003**
EF > 50 %, n (%)	837 (89.4)	967 (82.8)	**0.003**
LV-EDD*(mm), mean ± SD	56.4 ± 39.3	62.3 ± 39	**<0.001**
Aortic valve area (cm2), mean ± SD	0.7 ± 0.3	0.7 ± 0.5	0.7
Aortic valve area index, mean ± SD	0.4 ± 0.2	0.4 ± 0.3	0.9
Mean gradient (mmHg), mean ± SD	51.6 ± 17.3	49.8 ± 20.0	0.13
Isolated aortic regurgitation, n (%)	77 (8.2)	76 (6.6)	0.2
Isolated aortic stenosis, n (%)	522 (55.8)	668 (57.2)	0.6
Combined AR & AS, n (%)	337 (36)	423 (36.2)	0.9
Cardiac index, mean ± SD	3.0 ± 1.3	2.7 ± 1.1	**0.02**

EF* = ejection fraction. LVEDD* = left ventricular end-diastolic diameter.

4.1.3 Intraoperative Results

The intraoperative results of all patients are summarized in (Table 4.3). MIAVR group had significant longer procedural times. Patients in the CAVR group had significantly more blood transfusions. Low cardiac output syndrome was more likely to occur in the same group.

There were significant differences between the two groups in regard to the type of the implanted prosthesis. Patients in the CAVR were more likely to get biological and less mechanical prostheses than those in the MIAVR group. There were no significant differences in concomitant procedures between both groups.

Table 4. 3. Procedural data for all patients

	MIAVR	CAVR	*P*-value
All patients	**936**	**1167**	
Types of prostheses			
Biological prosthesis, n (%)	745 (79.6)	1008 (86.4)	**<0.001**
Mechanical prosthesis, n (%)	191 (20.4)	159 (13.6)	**<0.001**
Concomitant procedure(s)			
Ascending aorta repair, n (%)	83 (8.9)	117 (10)	0.23
Subvalvular myectomy, n (%)	301 (32.2)	359 (30.8)	0.85
Procedural times			
Aortic cross clamp time (min), mean ± SD	67.0 ± 18.5	62 ± 19.7	**<0.001**
Reperfusion time (min), mean ± SD	22.1 ± 9.4	18.9 ± 10.3	**<0.001**
CPB* time (min), mean ± SD	94.8 ± 25.0	85.7 ± 27.1	**<0.001**
Duration of surgery (min), mean ± SD	197.4 ± 44.4	174.7 ± 47.9	**<0.001**
Intraoperative blood transfusion			
Auto-Transfusion (ml), mean ± SD	940.2 ± 569.1	1033.5 ± 553.8	**<0.001**
Foreign blood (ml), mean ± SD	257.9 ± 105.5	314.1 ± 170.3	**<0.001**
Foreign plasma (ml), mean ± SD	246.4 ± 74.2	269.8 ± 73	0.9
Platelets concentrate (ml), mean ± SD	85.7 ± 8.9	86.4 ± 11.6	0.4
Low cardiac output, n (%)	9 (1.0)	28 (2.3)	**0.01**
Need for IABP*, n (%)	7 (0.7)	16 (1.4)	0.3
Intraoperative rhythm disturbance, n (%)	12 (1.3)	12 (1.0)	0.59

CPB* = cardiopulmonary bypass. Need for IABP* included the need for IABP during the surgery or after surgery (within the ICU-Stay).

4.1.4 Postoperative Results

4.1.4.1 Early postoperative outcomes (within the hospital stay)

Early postoperative results for all patients were summarized in (Table 4.3). Patients in the CAVR group needed significantly more blood transfusions after surgery. There were no significant differences between both groups in postoperative blood loss, mean hemoglobin level or the need for re-exploration for bleeding. CAVR patients also developed higher levels of serum creatinine and CK-levels and they had significantly more rhythm disturbances than patients in the MIAVR group. Additionally, postoperative pacemaker implantation was significantly more frequent in the CAVR group. The Intubation time, ICU-Stay and the hospital-stay were significantly shorter in the MIAVR group.

Table 4. 4. Early outcomes for all patients

	MIAVR	CAVR	*P*-value
All patients	**936**	**1167**	
Blood loss (ml/24h), median (IQR)	400 (225-650)	400 (250-700)	0.2
Re-exploration for bleeding, n (%)	46 (4.9)	44 (3.8)	0.3
Blood transfusion in ICU			
Auto-Transfusion (ml), mean ± SD	168.6 ± 50.3	235.1 ± 75	**0.005**
Foreign blood (ml), mean ± SD	630.3 ± 285	856.2 ± 407.2	**<0.001**
Foreign plasma (ml), mean ± SD	317.6 ± 98.4	402 ± 131.5	**0.04**
Platelets concentrate (ml), mean ± SD	114.3 ± 22.1	225.6 ± 43	**0.01**
Hemoglobin value (g/dl), mean ± SD	12.0 ± 1.8	11.9 ± 1.6	0.3
Creatinine level (mg/dl), mean ± SD	1.1 ± 0.8	1.2 ± 0.9	**<0.001**
CK (U/l) (highest value), median (IQR)	518 (357-741)	332 (208-547)	**<0.001**
CKMB (U/l) (highest value), median(IQR)	34 (26-46)	32 (21-46)	0.4
Postoperative rhythm disturbance			
Atrial arrhythmias (AF, SSS)*, n (%)	17 (1.8)	44 (3.8)	**0.002**
AVB* (all types), n (%)	26 (2.8)	59 (5.1)	**0,002**
AVB-III°, n (%)	21 (2.2)	38 (3.3)	0.16
Pacemaker implantation, n (%)	26 (2.7)	62 (5.3)	**0.014**
Intubation time (hours.), median (IQR)	8 (6-13)	9 (7-14)	**0.012**
ICU-Stay (days), median (IQR)	3 (2-5)	5 (3-8)	**<0.001**
Hospital stay (days), median (IQR)	9 (8-12)	11 (8-14)	**<0.001**

AF* = atrial fibrillation. SSS* = sick sinus syndrome. AVB* = atrio-ventricular block.

4.1.4.2 Late postoperative outcomes

Late postoperative outcomes for all patients are summarized in (Table 4.5). There were no significant differences in the need for sternum re-fixation (rewiring) and no difference in the rate of postoperative myocardial infarction between both groups.

Patients in the CAVR group developed a significantly higher incidence of renal and respiratory insufficiencies, cerebrovascular accidents, higher rate of need for redo surgery. 30-day and 1-year were significantly higher in this group. Moreover, the 5- and 10 years survival rates (illustrated with the Kaplan Meier curves Figure 4.1) were significantly higher in the MIAVR group.

Table 4. 5. Late outcomes for all patients

	MIAVR	CAVR	*P*-value
All patients	**936**	**1167**	
Sternum Re-fixation, n (%)	23 (2.5)	23 (2)	0.25
Renal insufficiency (Creatinine ≥ 1.5mg/dl), n (%)	107 (11.4)	196 (16.8)	**<0.001**
Need for hemodialysis, n (%)	31 (3.3)	70 (6)	**<0.001**
Respiratory insufficiency, n (%)	79 (8.4)	166 (14.2)	**<0.001**
Need for NIV*, n (%)	45 (4.8)	101 (8.7)	
Need for Re-intubation, n (%)	18 (1.9)	40 (3.4)	
Need for tracheostomy, n (%)	16 (1.7)	25 (2.1)	
Myocardial infarction, n (%)	3 (0.3)	7 (0.6)	0.36
Cerebrovascular accident, n (%)	15 (1.6)	48 (4.1)	**0.03**
Redo surgery (Re-AVR), n (%)	7 (0.7)	33 (2.8)	**<0.001**
Postoperative endocarditis, n (%)	5 (0.5)	26 (2.2)	
Postoperative paravalvular leak, n (%)	1 (0.1)	2 (0.2)	
Postoperative degenerative disease, n (%)	1 (0.1)	5 (0.4)	
Mortality rates			
30-day mortality, n (%)	14 (1.5)	39 (3.3)	**0.005**
1-year mortality, n (%)	27 (2.9)	83 (7.1)	**<0.001**
Overall mortality*, n (%)	44 (4.7)	184 (15.8)	**<0.001**

NIV* = non-invasive ventilation. Overall Mortality* included cardiac and non-cardiac causes.

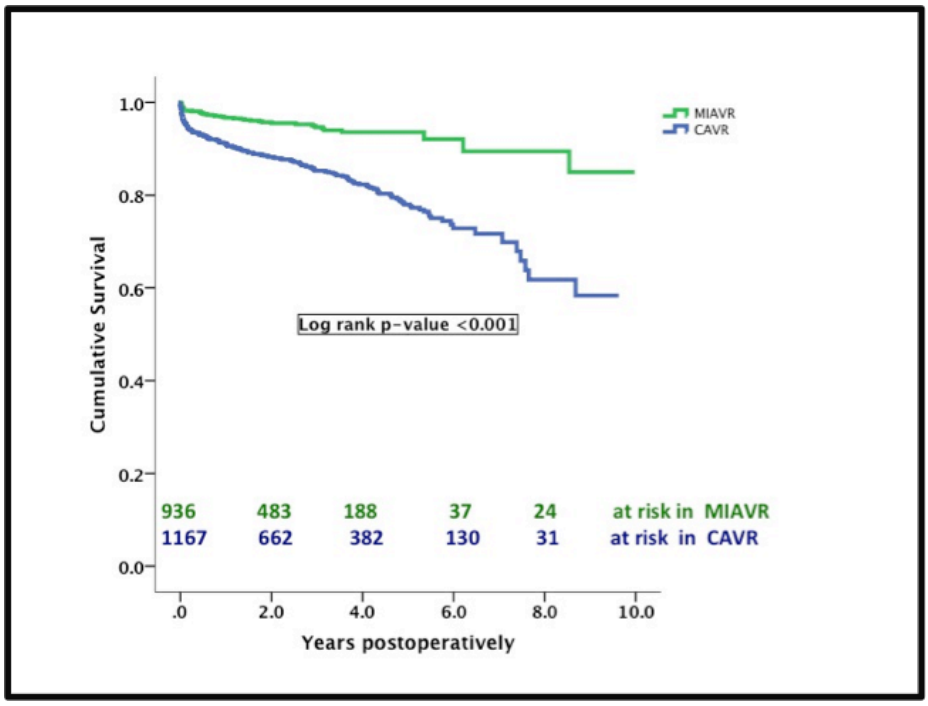

Figure 4. 1. Kaplan Meier survival curves for the patients before propensity matching

4.2 Results after Propensity Score Match (Matched patients)

4.2.1 Baseline (Demographic) Characteristics

The demographic characteristics after propensity matching are summarized in (Table 4.6). There were no more significant differences between the two matched subgroups in regard to age, sex, associated comorbidities and the surgical indication.

Table 4. 6. Demographic Characters for propensity matched patients

	MIAVR	CAVR	*P*-value
Propensity matched patients	**585**	**585**	
Age (years), mean ± SD	65.0 ± 10.5	65.7 ± 11.5	0.23
Female, n (%)	218 (37.2)	218 (37.2)	0.9
Body mass index (Kg/m²), mean ± SD	27.2 ± 4.2	27.4 ± 4.9	0.48
Diabetes mellitus, n (%)	58 (9.9)	63 (10.7)	0.9
Systemic hypertension, n (%)	310 (53)	327 (55.9)	0.3
Peripheral vascular disease, n (%)	11 (1.9)	12 (2.1)	0.84
Previous peripheral vascular bypass, n (%)	16 (2.7)	10 (1.7)	0.17
Previous myocardial infarction, n (%)	15 (2.5)	13 (2.2)	0.85
Previous PTCA/Stent implantation, n (%)	31 (5.3)	19 (3.3)	0.1
Preoperative pacemaker, n (%)	15 (2.5)	13 (2.2)	0.85
Chronic pulmonary disease*, n (%)	56 (9.5)	55 (9.4)	0.9
Previous cerebrovascular accident, n (%)	14 (2.4)	20 (3.4)	0.3
Creatinine (mg/dl), mean ± SD	0.9 ± 0.4	0.9 ± 0.3	0.4
Renal insufficiency (Creatinine ≥ 1.5mg/dl), n (%)	32 (5.5)	23 (4.0)	0.2
CK value (U/l), median (IQR)	79 (52-123)	48 (25-83)	<0.001
CKMB value (U/l), median (IQR)	7 (6.3-10)	7 (5-13.5)	0.6
Hemoglobin level (g/dl), mean ± SD	13.7 ± 1.4	13.6 ± 1.5	0.4
Surgical indication			
Elective, n (%)	515 (88.1)	517 (88.4)	0.9
Urgent, n (%)	70 (11.9)	68 (11.6)	0.9

Chronic pulmonary diseases* included chronic obstructive and restrictive diseases.

4.2.2 Echocardiographic Data

The echocardiographic data after propensity matching are summarized in (Table 4.7). There were no more significant differences between the two matched subgroups in regards to left ventricular function, left ventricular end-diastolic diameter, and the aortic valve area or gradient.

Table 4. 7. Echocardiographic data for propensity matched patients

	MIAVR	**CAVR**	***P*-value**
Propensity matched patients	**585**	**585**	
LV-Function			
EF* <35 %, n (%)	25 (4.3)	25 (4.3)	0.9
EF 35-50 %, n (%)	58 (9.9)	63 (10.7)	0.9
EF > 50 %, n (%)	502 (85.8)	497 (85)	0.9
LV-EDD* (mm), mean ± SD	57.2 ± 39.2	60.2 ± 39	0.19
Aortic valve area (cm2), mean ± SD	0.7 ± 0.4	0.7 ± 0.5	0.65
Aortic valve area index, mean ± SD	0.4 ± 0.2	0.4 ± 0.2	0.65
Mean gradient, (mmHg) mean ± SD	50.7± 16.9	50.7 ± 21.1	0.96
Isolated aortic regurgitation, n (%)	65 (11.1)	44 (7.5)	0.04
Isolated aortic stenosis, n (%)	310 (53)	327 (55.9)	0.3
Combined AR & AS, n (%)	210 (35.9)	214 (36.6)	0.8
Preoperative cardiac index, mean ± SD	3.0 ± 1.3	2.8 ± 1.1	0.25

EF* = ejection fraction. LVEDD* = left ventricular end-diastolic diameter.

4.2.3 Intraoperative Results

Intraoperative results after propensity matching are summarized in (Table 4.8). The whole surgical, CPB and reperfusion times were significantly shorter in CAVR procedure. However, the aortic cross clamp times were similar in both subgroups. Autologous-transfusions during surgery were still significantly higher in the CAVR subgroup. Concomitant subvalvular myectomy was significantly higher in MIAVR subgroup. Additionally, there was a significant difference between both subgroups in the type of the implanted prosthesis. There were no more significant differences between the two subgroups in regard to the incidence of low cardiac output syndrome, rhythm disturbance or the rate of pacemaker implantation.

Table 4. 8. Procedural data for propensity matched patients

	MIAVR	CAVR	*P*-value
Propensity matched patients	**585**	**585**	
Types of prostheses			
Biological prosthesis, n (%)	493 (84.3)	444 (75.9)	**0.001**
Mechanical prosthesis, n (%)	92 (15.7)	141 (24.1)	**0.001**
Concomitant procedure(s)			
Ascending aorta repair, n (%)	52 (8.9)	77 (13.2)	0.6
Subvalvular myectomy, n (%)	189 (32.3)	152 (26)	**0.03**
Procedural times			
Aortic cross clamp time (min), mean ± SD	65.6 ± 18.4	64.3 ± 19.8	0.25
Reperfusion time (min), mean ± SD	22.3 ± 10.0	19.0 ± 11.1	**<0.001**
CPB* time (min), mean ± SD	93.5 ± 25.0	88.0 ± 28.0	**<0.001**
Duration of surgery (min), mean ± SD	196.9 ± 45.6	176.8 ± 45.8	**<0.001**
Intraoperative blood transfusion			
Auto-Transfusion (ml), mean ± SD	927.2 ± 425.6	1036.4 ±599.6	**<0.001**
Foreign blood (ml), mean ± SD	271 ± 111.9	244.7 ± 108.6	0.83
Foreign plasma (ml), mean ± SD	267.3 ± 86.3	228.3 ± 50.4	0.16
Platelets concentrate (ml), mean ± SD	96.5 ± 9.2	90.7 ± 7.2	0.63
Low cardiac output syndrome, n (%)	6 (1.0)	13 (2.2)	0.14
Need for IABP*, n (%)	4 (0.7)	8 (1.3)	0.36
Intraoperative rhythm disturbance, n (%)	8 (1.3)	3 (0.5)	0.14

CPB* = Cardiopulmonary bypass. Need for IABP* included the need for IABP during the surgery or after surgery (within the ICU-Stay).

4.2.4 Postoperative Results

4.2.4.1 Early postoperative outcomes (within the hospital stay)

Early postoperative outcomes after propensity matching are summarized in (Table 4.9). Again, there was a significant higher rate of Autologous-blood transfusion in CAVR subgroup, and they still had a significantly longer intubation time. Meanwhile, ICU- and hospital stay were no longer significantly longer in the same subgroup.

There were no more significant differences between both subgroups regarding the serum creatinine and CK levels, the incidence of rhythm disturbance or the need for pacemaker implantation. Once again there were no significant differences in the amount of blood loss, mean hemoglobin level or the need for re-exploration for bleeding between both subgroups.

Table 4. 9. Early outcomes for propensity matched patients

	MIAVR	**CAVR**	***P*-value**
Propensity matched patients	**585**	**585**	
Blood loss (ml/24h), median (IQR)	400 (224-683)	400 (250-610)	0.83
Re-exploration for bleeding, n (%)	31 (5.3)	20 (3.4)	0.34
Blood transfusion in ICU			
Auto-Transfusion (ml), mean ± SD	170.2 ± 47.6	243.5 ± 89.3	**< 0.001**
Foreign blood (ml), mean ± SD	664.9 ± 301.7	615.5 ± 257.6	0.25
Foreign plasma (ml), mean ± SD	335.1 ± 104.8	312.4 ± 92.8	0.53
Platelets concentrate (ml), mean ± SD	194.6 ± 24.4	217.3 ± 36.4	0.23
Hemoglobin value (g/dl), mean ± SD	12.0 ± 1.9	11.8 ± 1.5	0.09
Creatinine level (mg/dl), mean ± SD	1.1 ± 0.7	1.0 ± 0.7	0.24
CK (U/l) (highest value), median (IQR)	518(364-753)	488(248-629)	0.83
CKMB (U/l) (highest value), median(IQR)	33 (26-45)	33 (22-49)	0.15
Postoperative rhythm disturbance			
Atrial arrhythmias (AF, SSS)*, n (%)	13 (2.2)	14 (2.4)	0.38
AVB* (all types), n (%)	14 (2.4)	24 (4.1)	0.38
AVB-III, n (%)	14 (2.4)	21 (3.6)	0.24
Pacemaker implantation, n (%)	19 (3.2)	28 (4.8)	0.17
Intubation time (hours), median (IQR)	7 (5-11)	8 (6-14)	**0.01**
ICU-Stay (days), median (IQR)	3 (2-5)	4 (3-6)	0.35
Hospital stay (days), median (IQR)	9 (8-12)	10 (8-13)	0.23

AF* = atrial fibrillation. SSS* = sick sinus syndrome. AVB* = atrio-ventricular block.

4.2.4.2 Late postoperative outcomes

The late postoperative outcomes after propensity matching are summarized in (Table 4.10). Again, there were significant higher incidences of renal and respiratory insufficiencies in the CAVR subgroup. Once again, there was no significant difference in the need for sternum rewiring or the incidence of myocardial infarction. There were no more significant differences between both subgroups regarding to cerebrovascular accidents, the need for redo surgery, the 30-day and 1-year mortality rates. The 5- and 10-years survival rates (illustrated in the Kaplan Meier curves Figure 4.2) were no more significantly different between both subgroups.

Table 4. 10. Late outcomes for propensity matched patients

	MIAVR	**CAVR**	***P*-value**
Propensity matched patients	**585**	**585**	
Sternum Re-fixation, n (%)	12 (2.1)	16 (2.7)	0.38
Renal insufficiency (Creatinine ≥ 1.5mg/dl), n (%)	53 (9.0)	94 (16.0)	**< 0.001**
Need for hemodialysis, n (%)	15 (2.5)	26 (4.4)	
Respiratory insufficiency, n (%)	50 (8.5)	69 (11.8)	**0.03**
Need for NIV*, n (%)	27 (4.6)	45 (7.7)	
Need for Re-intubation, n (%)	10 (1.7)	17 (2.9)	
Need for tracheostomy, n (%)	13 (2.2)	7 (1.2)	
Myocardial infarction, n (%)	2 (0.3)	3 (0.5)	0.67
Cerebrovascular accident, n (%)	11 (1.9)	16 (2.7)	0.29
Redo surgery (Re-AVR), n (%)	5 (0.9)	13 (2.2)	0.14
Postoperative endocarditis, n (%)	2 (0.3)	9 (1.5)	
Postoperative paravalvular Leak, n (%)	2 (0.3)	0 (0)	
Postoperative degenerative disease, n (%)	1 (0.2)	4 (0.7)	
Mortality rates			
30-day mortality, n (%)	9 (1.5)	10 (1.7)	0.74
1-year mortality, n (%)	18 (3.1)	28 (4.8)	0.12
Overall mortality*, n (%)	27 (4.6)	65 (11.1)	**<0.001**

NIV* = non-invasive ventilation. Overall Mortality* included non-cardiac causes as well.

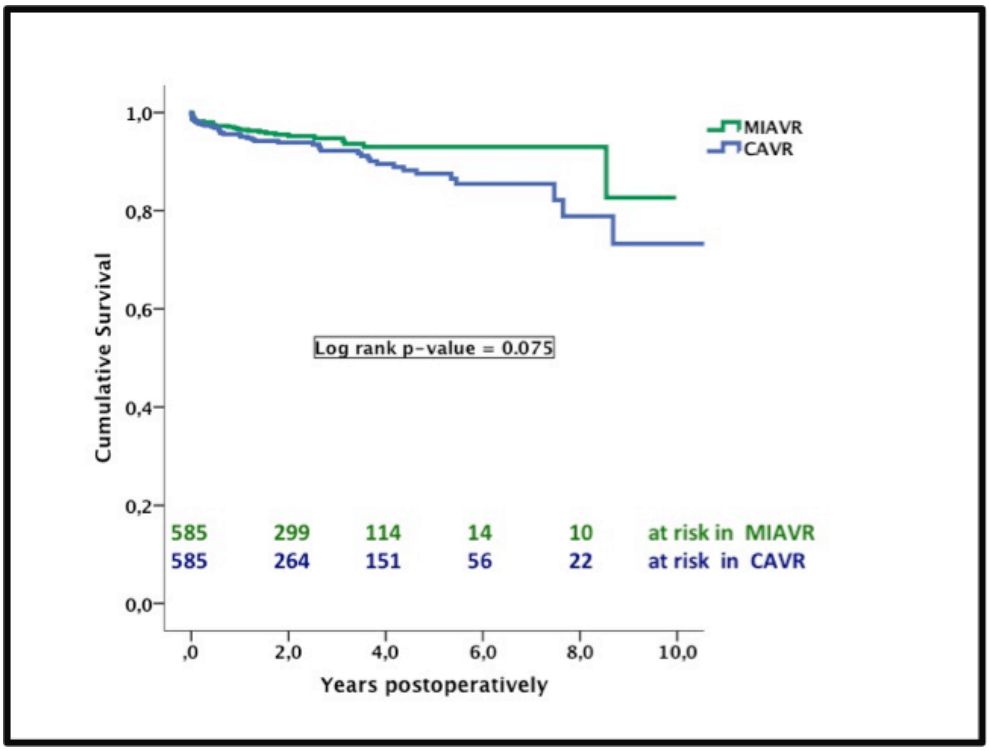

Figure 4. 2. Kaplan Meier survival curves for the patients after propensity matching

5. Discussion

5.1 Discussion of Methods

Usually, the final decision upon the operative plan, including surgical approach, is taken during the meeting before surgery and is a team-shared opinion that takes multiple factors in consideration. In most cases, the preoperative patients' data influence the decision of the operative approach such as (age, sex, weight, comorbidities and severity of the aortic disease as well as the heart function). In fact, most of CAVR patients tend to be older, more females, more associated comorbidities and lower cardiac function. In these patients, a faster surgery and shorter CPB time is recommended in order to minimize intra- and postoperative complications.

Based on that, the choice of operative technique is a result of application of our internal guidelines recommendations to each single patient, and is not a surgeon's personal preference. This created a sort of bias between the two groups of patients. This bias made the comparison between both groups quite unfair. Similarly, other investigators such as (Bang et al., 2012; Furukawa et al., 2014; Gilmanov et al., 2013; Glauber et al., 2013; Sharony et al., 2004) experienced similar problem in their studies where there was a significant difference in the baseline and echocardiography characteristics between both groups. Accordingly, these investigators developed a propensity score match to mitigate bias between the two groups.

Similar to the previous studies, which used propensity score match in comparing MIAVR and CAVR, we applied it to reduce the bias between the two groups of patients in our study as well. A propensity score-matched sample consists of pairs of treated and untreated subjects, matched on the propensity score. Therefore, no systematic differences in baseline characteristics between treated and untreated subjects may be expected. However, propensity score balances only measured baseline variables between treatment modalities and subjects may still be imbalanced on unmeasured characteristics. Ongoing controversy exists as to which variables should be included in the propensity score model (Austin, 2008, 2009). In the present study, the following parameters were included: age, gender, weight, height, preoperative serum creatinine level, previous myocardial infarction, left ventricular function and aortic valve pathology. We believe that those parameters played an important role in procedural selection and were also responsible for a selection bias between both accesses.

5.2 Discussion of Results

5.2.1 Baseline Characteristics

The current study had shown a statistically significant difference between the CAVR and MIAVR groups regarding age, gender and comorbidities. The patients in the CAVR group were older (about 8 years), included more females and were more associated with comorbidities. In addition, patients in the CAVR group exhibited a higher rate of LV dysfunction (EF ≤ 35% in 5.6% vs. 3% of the patients, p=0.003, respectively). These results are similar to those reported from other investigators (Bakir et al., 2006; Doll et al., 2002; Raja, Benedetto, & Amrani, 2013). They observed that patients undergoing CAVR were significantly older (5-7 years older) and they were more likely to have associated comorbidities and had higher rates of LV-dysfunction. They conclude that the reason for such differences was mainly a surgeon's patient selection, since the type of operative approach depended entirely from the discretion of the surgeon.

The higher the rate of associated comorbidities, the more LV-dysfunction and the age of the patients in the CAVR group is a possible explanation for the higher risk of intra and postoperative complications, postoperative morbidities and death. Accordingly, for these patients a fast surgery, with short CPB and cross-clamp times was needed, in order to reduce the operative risk. In the CAVR group there were also a significantly higher number of patients who needed surgery on an urgent basis. These differences in the baseline characteristics created a kind of bias between both groups making the comparison of outcomes uneven.

For this reason, these differences in the baseline characteristics were adjusted by developing a propensity score matching to reduce the effect of selection bias and potential confounding. After performing a propensity score match, there were no more significant differences in regards to age, gender, associated comorbidities, LV-function or indication for urgent surgery between the two subgroups. Similar studies have been published; showing that after performing a propensity score match, significant differences in the baseline characteristics could be eliminated (Bang et al., 2012; Furukawa et al., 2014; Gilmanov et al., 2013).

5.2.2 Procedural Data

Cross-clamp and CPB times: In our experience, the MIAVR approach was significantly more time consuming than the CAVR procedure. In case of MIAVR, we found that mean aortic cross clamp

time, mean CPB time and total operation time were 5 minutes, 9 minutes and 23 minutes longer, respectively. Other investigators reported similar findings (Cooley, 1998; Doll et al., 2002), they observed an average increase of 5 minutes in the aortic cross clamp time and 14 minutes for the total surgery time during MIAVR procedures. On the other hand, other investigators (Bakir et al., 2006) have reported longer cross-clamp and CPB times in the CAVR group.

Although, retrospective studies (Liu, Sidiropoulos, & Konertz, 1999; Vanoverbeke et al., 2004) as well as prospective randomized studies (Aris et al., 1999; Bonacchi et al., 2002) demonstrated that the cross clamp and CPB times were similar for both procedures, our results reported after propensity matching similar aortic cross clamp times in MIAVR and CAVR procedures (65.6±18.4 vs. 64.3±19.8 min, p=0.25) and significant longer CPB times in the MIAVR procedure (93.5±25 vs. 88±28 min, p<0.001). A possible explanation for our results could be due to the more complexity and technical demanding of the MIAVR procedure in comparison to the CAVR procedure, due to the limited exposure and the little space to operate as well as the effect of the learning curve of the operating surgeons.

Types of prostheses: Our study shows a significant difference between the types of the prostheses implanted in both groups. The initial results show a significantly higher rate in the use of biological prostheses in the CAVR than MIAVR group (86.4% vs. 79.6%, p<0.001), and a significantly lower rate of mechanical prostheses implantation in both groups (13.6% vs. 20.4%, p<0.001, respectively). However, after performing propensity matching we found a significant higher rate of the implanted biological prostheses in the MIAVR subgroup (84.3% vs. 75.9%, p<0.001) and a significant lower rate of the implanted mechanical prostheses in the same subgroup (15.7% vs. 24.1%, p<0.001, respectively).

Doll and colleagues reported a non-significant difference between MIAVR and CAVR in regard to the type of the prostheses used, but the rate of the implanted mechanical prostheses (55% and 52%, p=0.8) was higher in both groups than the implanted bioprostheses (45% and 47%, p=0.8 respectively) (Doll et al., 2002). Bakir and associates also found no significant differences in the type of the used prostheses between MIAVR and CAVR groups, but the rate of the implanted bioprostheses was higher in both groups (76.6% and 79.2%, p=0.75) than the rate of the implanted mechanical prostheses (23.3% and 20.8%, p=0.55) (Bakir et al., 2006). A possible explanation for these differences might be attributed to the age of each patient, which according to the guidelines recommends implantation of mechanical prosthesis for the patients younger than 65 years and biological prosthesis for the patients older than 65 years (American College of et al., 2006).

Procedural complications: Although a significantly higher incidence of postoperative low-output syndrome in the CAVR group was found (2.3% vs. 1%, p=0.01), there was no significant difference in the rate of IABP implantation in both groups. Other investigators demonstrated similar results; Bakir and colleagues for example, reported in their study a non-significant difference in the need for IABP between both groups (0.4% vs. 0, p=0.35) (Bakir et al., 2006). In contrast, Raja and associates reported a significantly higher rate for the need of IABP in CAVR group than MIAVR (4.34% vs. 0.59%, p=0.03) (Raja et al., 2013). In our study, the reason for the higher rate of low cardiac output syndrome in CAVR group may be related to the higher rate of LV-dysfunction (EF ≤ 35%) in this group in comparison to MIAVR group (5.6% vs. 3% of patients, respectively).

After propensity matching, our results showed a non-significant difference between MIAVR and CAVR subgroup in the incidence of low cardiac output (1% vs. 2.2%, p=0.14) or the need for IABP (0.7% vs. 1.3%, p=0.36, respectively). Recent studies, which also performed a propensity matching, reported similar results. Gilmanov et al. reported an incidence of low output syndrome in 1.1% and 0.5% of the patients respectively (Gilmanov et al., 2013). Furukawa and associates reported an incidence of low output syndrome in 2% and 3% of the patients respectively, and the need for the IABP was only in 1% of the patients in both groups (Furukawa et al., 2014).

5.2.3 Early Postoperative Course

Bleeding and blood transfusion: In spite of the significantly higher blood (autologous or foreign) in the CAVR than MIAVR group, there was no significant difference in the postoperative blood loss (median value of 400 ml/24h), the rate of re-explorations for bleeding (3.8% vs. 4.9%, respectively, p=0.3) or the mean postoperative hemoglobin level (11.9±1.6 vs. 12.0±1.8, p=0.3, respectively) in both groups. Similar to our results, other studies reported that there was also a non-significant difference in the rates of re-exploration for bleeding between both groups. Doll and associates reported that 9% of the CAVR group and 7% of the MIAVR group needed a re-exploration for bleeding (p=0.4) (Doll et al., 2002). Bakir and colleagues reported that the rate of re-exploration for bleeding was 6.2% in the CAVR group and 7.8% in the MIAVR group (p=0.5), even if there was a significantly higher rate of blood loss in the CAVR than MIAVR group (1172 ± 999 ml vs. 952 ± 929 ml, p<0.005, respectively) (Bakir et al., 2006). Vanoverbeke and associates also found a similar incidence of re-exploration for bleeding in the MIAVR group with 7.5% (Vanoverbeke et al., 2004). Raja et al. reported that 7.6% of the CAVR group and 6.6% of the MIAVR group needed a re-exploration for bleeding (p=0.79) (Raja et al., 2013).

After propensity matching, our study found a significantly higher rate of intra-and postoperative autologous-blood transfusion in the CAVR group. However, the rate of foreign blood transfusions became no longer significantly different. A non-significant difference in the amount of blood loss, re-explorations for bleeding and the postoperative mean level of hemoglobin was noticed again. Different results were reported in Literature by other investigators who apply propensity matching, Bang and colleagues reported a non-significant difference between the MIAVR and CAVR groups in the amount of blood loss (399±360 ml vs. 433±324 ml, *p*=0.53 respectively), and the amount of blood transfusions (680 ± 826 ml vs. 633 ± 738 ml, *p*=0.7, respectively), and the incidence of re-exploration for bleeding in both groups (9.6% and 8.2%, *p*=0.77, respectively) (Bang et al., 2012). Gilmanov et al. reported a non-significant lower incidence of re-exploration for bleeding in the MIAVR than the CAVR group (4.4% vs. 6%, *p*=0.63), but significantly higher rate in the amount of blood transfusion in the CAVR group (2 blood pack unites vs. 1 blood pack unit, *p*=0.046, respectively) (Gilmanov et al., 2013). Most recently, Furukawa et al. reported also the same incidence of re-exploration for bleeding with 6% in both groups (Furukawa et al., 2014).

A possible explanation for the less blood transfusion intra- and early postoperatively in the MIAVR procedure might be attributed to the smaller incision, which theoretically reduces the amount of bleeding and transfusion requirements (Gilmanov et al., 2013). The lower rates of postoperative re-exploration for bleeding in our study (3.8% in CAVR vs. 4.9% in MIAVR) in comparisons with the above mentioned studies might be due to the meticulous attention to hemostasis during the procedure.

Postoperative arrhythmias: In our study, the incidence of heart arrhythmias (Atrial arrhythmias and AVB) was significantly higher in the CAVR than MIAVR group (3.8% and 5.1% vs. 1.8% and 2.8%, *p*=0.002, respectively) same as the need for pacemaker implantation (5.3% vs. 2.7%, *p*=0.014, respectively). On the contrary, Doll, Bakir, Raja and their associates reported a non-significant difference in the incidence of atrial fibrillation or pacemaker implantation between both groups (Bakir et al., 2006; Doll et al., 2002; Raja et al., 2013). Bakir explained that the high incidence of new-onset AF observed in CAVR and MIAVR groups (27.3% vs. 31%, *p*=0.44) was age related, as about 50% of the patients included in his study were older than 70 years.

However, after applying propensity matching, we found non-significant higher rates in the incidence of postoperative arrhythmias (Atrial arrhythmias and AVB) in the CAVR than the MIAVR subgroup (2.4 and 4.1% vs. 2.2% and 2.4%, *p*= 0.38, respectively), same as the need for pacemaker implantation (4.8% vs. 3.2%, *p*= 0.17). Bang and colleagues, reported similar results

with non-significance difference in the incidence rate of postoperative arrhythmias after propensity score matching as well (Bang et al., 2012). On the other hand, Gilmanov and associates reported a significantly higher rate of the incidence of heart arrhythmias as well as the rate of pacemaker implantation in the CAVR group after propensity matching (Gilmanov et al., 2013), he attributed the lower incidence of AF in the MIAVR group to the large number of patients who had AVR through a small lateral minithoracotomy. Attributing that to this kind of approach, which seems to be associated with a lower incidence of postoperative AF, which reported in an earlier study (Glauber et al., 2013). A possible explanation of our results is that the older age of the patients in the CAVR group before propensity matching was an independent risk factor for postoperative AF (European Heart Rhythm et al., 2010). The significant difference in the age was eliminated between both groups after performing the propensity score match in our study; hence the incidence of postoperative arrhythmias was also no more statistically significant.

Intubation time, ICU-and hospital stay: Our results showed that the patients in the MIAVR group had a significantly shorter intubation times and shorter ICU-and hospital stay. A reduction of intubation time facilitates an early mobilization and discharge from the ICU, and early discharge from the hospital as well. A decrease of the length of stay is an important aspect of resource use, since ICU and hospital stay are the major determinants of the cost after cardiac surgery (Hamilton, Norris, Wensel, & Koshal, 1994). Several studies had also demonstrated reduced hospital stay and costs for minimal access AVR when compared with conventional AVR (Doll et al., 2002; Liu et al., 1999; Raja et al., 2013; Svensson & D'Agostino, 1998; Vanoverbeke et al., 2004).

After propensity matching, our results demonstrated a significant shorter intubation time in the MIAVR subgroup (median of 7 vs. 8 hours, p=0.01), but a non-significant shorter ICU- and hospital stay in the same subgroup (3 vs. 4 days, p=0.35, and 9 vs. 10 days, p=0.23, respectively). Some investigators reported a significant shorter intubation time and hospital stay in the MIAVR group after propensity matching (Gilmanov et al., 2013; Glauber et al., 2013). However, Furukawa et al., Bang et al. reported similar intubation times and hospital stay in both groups (Bang et al., 2012; Furukawa et al., 2014), Furukawa explained that the duration of hospitalization was determined by reimbursement issues based on the diagnosis-related groups (DRGs) system in Germany. The discrepancy among these studies might be explained by the different level of experience of each center for postoperative patients' care. As the preoperative differences in the comorbidities were diminished after propensity score matching between both groups, this might be a possible explanation of our results. It must also be considered, that we do not favor early discharge during the process of adjusting anticoagulation regimen.

5.2.4 Morbidity and Mortality

Sternum re-fixation (rewiring): Before propensity matching, our study showed a non-significant difference in the incidence of sternum re-fixation in CAVR and MIAVR groups (2 vs. 2.5%, p=0.25). Our results were confirmed after propensity matching where the incidence rate of sternum rewiring was still similar in both subgroups (2.7 vs. 2.1%, p=0.38, respectively).

Other investigators (Bakir et al., 2006; Doll et al., 2002; Raja et al., 2013) reported a non-significant difference in the incidence of sternal wound infection between both groups. Other investigators who apply propensity matching (Bang et al., 2012; Gilmanov et al., 2013; Glauber et al., 2013) reported also a non-significant difference in the incidence of sternal wound infection in both groups. The above-mentioned investigators commented only on the sternal wound infections and did not mention the incidences of sternum rewiring which in our study was considered as a strong indicator of postoperative deep wound infections.

Embolic complications: Although (Cooley, 1998; Vanoverbeke et al., 2004) reported that the difficulty of air removal from the heart at the end of surgery is one of the major concerns about MIAVR procedures, our results reported a non-significant difference in the incidence rate of air removal complications such as myocardial infarction and CKMB-level between both groups before propensity matching. On the other hand, we found a significant higher rate of incidence of postoperative cerebrovascular events (delirium, transient ischemic attacks and strokes) in the CAVR group (4.1% vs. 1.6%, p=0.03). This might be attributed to the well-known fact that the risk of postoperative stroke has been shown to be nearly threefold higher for patients with postoperative atrial fibrillation (Hogue & Hyder, 2000; Taylor et al., 1987), our study reported that the incidence of Atrial arrhythmias was significantly higher in the CAVR group before applying propensity matching (3.8% vs. 1.8%, p=0.002, respectively).

However, after propensity matching, our study did not reveal any significant difference in the CK- or CKMB-levels, or incidence of postoperative cerebrovascular events or myocardial infarction between both subgroups. We believe that flooding the operative filed with carbon dioxide, aortic needle aspiration, and TEE confirmation of the absence of air bubbles were sufficient to achieve meticulous air removal from the left ventricle in the patients in MIAVR procedure. Similar to our results, other investigators (Bang et al., 2012; Furukawa et al., 2014; Gilmanov et al., 2013; Glauber et al., 2013) reported a non-significant difference in the rate of incidence of postoperative myocardial infarction or cerebrovascular accidents after performing propensity matching.

Renal insufficiency: Before propensity matching, and in contrast with the results of other studies which reported non-significant differences in the incidence of postoperative renal insufficiency and the need for hemodialysis (Bakir et al., 2006; Raja et al., 2013), our study reported a significant lower level of the mean postoperative serum creatinine, lower rate of renal insufficiency (creatinine ≥1.5mg/dl), and need for hemodialysis in MIAVR group. In addition to the well-known fact that the patients undergoing cardiac surgery have a 3.3-folds increased risk of postoperative acute kidney injury and 2.3-folds increased risk of requiring hemodialysis (Lenihan, Montez-Rath, Mora Mangano, Chertow, & Winkelmayer, 2013), a possible explanation for our findings is that the patients in the CAVR group were significantly older and presented with more comorbidities including preoperative renal insufficiency than the patients in the MIAVR group.

After propensity matching, our results showed a non-significant difference in the mean level of serum creatinine among both subgroups, but a significant higher rate of postoperative renal insufficiency (creatinine ≥1.5mg/dl), and the need for hemodialysis in CAVR subgroup (16% vs. 9% and 4.4% vs. 2.5%, $p<0.001$, respectively). Others who performed a propensity matching in their studies (Bang et al., 2012; Furukawa et al., 2014; Gilmanov et al., 2013) reported a non-significant difference in the incidence of postoperative renal insufficiency or the need for hemodialysis between both groups. A clear explanation of our results could not be found. The results might be attributed to other factors such as preoperative creatinine clearance level or glomerular filtration rates, which where not evaluated for the patients before the surgery, besides the presence or absence of preoperative diabetic or hypertensive nephropathies that also were not evaluated for the patients in both groups. Finally, One could speculate that shorter ventilation time and earlier mobilization in the MIAVR group might have contributed to better renal function.

Respiratory complications: We also found a significantly lower rate of respiratory insufficiency (need for NIV, re-intubation or tracheostomy) in the MIAVR than the CAVR group (8.4 vs. 14.2%, $p=0.001$). Other investigators (Doll et al., 2002; Raja et al., 2013) reported similar results with significant lower rate of respiratory complications in MIAVR group.

The significantly lower rate of respiratory insufficiency in MIAVR group was confirmed in our study after propensity matching (8.5 vs. 11.8%, $p=0.03$, respectively). Bang et al., Gilmanov et al. reported in their studies a non-significant difference in the rate of respiratory complications between groups after propensity matching (Bang et al., 2012; Gilmanov et al., 2013). The discrepancy between our results and other studies might be due to the difference in the experience between the centers in postoperative patients' care. Our findings might be explained by the shorter intubation time in the MIAVR group, which reduces the risk of respiratory infections. In addition

to that, the increased stability of the thoracic cage after upper partial ministernotomy and increased integrity of the pleural cavities allowed patients to be mobilized early and cough more efficiently, this was also reported by others (von Segesser et al., 1999). The significant reduction of postoperative lung function is not only influenced with the use of CPB but also by the length of incision (Bonacchi et al., 2002; Hallfeldt, Siebeck, Thetter, & Schweiberer, 1995).

Re-Operations: In our study, 2.8% of the patients in CAVR group and 0.7% of the patients in MIAVR group required redo aortic valve replacement after the first surgery (Re-AVR). This significant difference (p<0.001) was not confirmed after performing propensity matching. A possible explanation for this could be attributed to the preoperative patients' general status. Patients in the CAVR group were older and had more comorbidity, and this might have made such patients more vulnerable for endocarditis, which represented the main causes for Re-AVR before (2.2% vs. 0.5%) and after (1.5% vs. 0.3%) propensity matching.

Bakir and colleagues reported a non-significant difference in the incidence of postoperative endocarditis between CAVR and MIAVR groups with incidence rate of 0.4% and 0% respectively (p=0.35) (Bakir et al., 2006). In our study, paravalvular leak played less important role in postoperative valve dysfunctions before (0.2% vs. 0.1%) and after (0% vs. 0.3%) propensity matching respectively. Borman et al., Christiansen et al. reported a range of incidence of paravalvular leakage from 0% to 4.4 % (Borman et al., 1998; Christiansen et al., 1999). Meanwhile, our study showed higher incidence rate of valve degeneration before (0.4% vs. 0.1%) and after (0.7% vs. 0.2%) propensity matching in the CAVR group as well.

Mortality: Finally, our study revealed that 30-day and 1-year mortality rates were significantly lower in the MIAVR group (1.5% vs. 3.3% and 2.9% vs. 7.1%, p<0.001, respectively), and the 5- and 10-years survival rates were significantly higher in the same group, which illustrated by Kaplan Meier curves (Figure 4.1). However, when we accounted for the risk factors (i.e. age, sex, comorbidities) after performing propensity matching, MIAVR was no longer a predictor of better survival. It is therefore evidence that the difference in early mortality rates between both groups was due to differences in baseline characteristics. In spite of that, other studies (Bakir et al., 2006; Raja et al., 2013) reported a non-significant difference in the mortality rate between both groups even with significant difference in the baseline characteristics.

After propensity matching, the early mortality rates were non-significantly lower in MIAVR subgroup (1.5% vs. 1.7%, p=0.74 in 30-day mortality and 3.1% vs. 4.1%, p=0.12 in 1-year

mortality, respectively), additionally, the 5-and 10 years survival rates were also no more significantly higher in the same subgroup, which illustrated by Kaplan Meier curves (Figure 4.2). Other researchers who performed a propensity matching have also reported a non-significant difference in mortality rates in their studies (Furukawa et al., 2014; Gilmanov et al., 2013; Glauber et al., 2013). Although, overall mortality was significantly higher in CAVR group and subgroup before and after propensity matching, we did not take it as predictor of survival as it included cardiac and non-cardiac causes.

5.3 Study Limitations

This is a retrospective, single center, observational study of patients collected from our database; thus it reflects a single-center experience only. It includes all the patients who underwent first-time MIAVR or CAVR at our institution. All our surgeons, including young surgeons during their training, performed surgery. The learning curve may have an effect on surgery duration, aortic-cross clamp and CPB times.

Since many of the patients included in the study underwent the surgery long time ago and some of them were foreigners (about 2% of each group) who travelled back to their countries early after surgery, follow up was only 98% completed as these patients were lost in the last follow up.

Preoperative data such as EuroSCORE (Appendix, Table 8.2) was not calculated for all patients and documented in our database only after the year 2008 and it was difficult to calculate it for the rest of patients years after surgery, due to the huge number of the patients participated in this study. That's why it was excluded from the propensity matching evaluation in this study. Diabetic or hypertensive nephropathies were not evaluated in our study as well, and the preoperative serum creatinine level was the one indicator reflecting the preoperative renal function in this study, this might affect the incidence of the postoperative renal insufficiency.

Additionally, some results such postoperative pain, wound cosmetics, patient satisfaction and cost-effectiveness were difficult to be reported so directly in our study, as many of the surgeries were performed long time ago. These results have been considered as the main advantages of MIAVR over CAVR in earlier studies (Bang et al., 2012; Bonacchi et al., 2002; Doll et al., 2002; Tabata et al., 2008; von Segesser et al., 1999). Nevertheless, we could evaluate some of these results indirectly, by assessing other parameters, which gave us an idea about these results. For example, the shorter intubation time, in addition to the less blood loss in MIAVR group allowed the removal

of the chest tubes early after surgery and both allowed early mobilization of the patients which so reduces the pain produced by prolonged bedridden and gave such patients a satisfactory feeling of fast getting back to the normal habits. The smaller the size of incision in MIAVR group gave us an idea about the wound cosmetics. Finally, the shorter ICU-and hospital-stay played an important indirect role to reduce the overall cost of MIAVR procedures.

5.4 Conclusion

Before applying propensity matched analysis, the main findings of this study were: 1) Patients in the CAVR group were significantly older and presented with significantly more comorbidities than those in the MIAVR group. 2) The surgical and CPB times were significantly longer in MIAVR procedure. 3) Patients in the CAVR group needed significantly more blood transfusions. 4) The incidence of postoperative complications (low cardiac output syndrome, rhythm disturbance, cerebrovascular accidents, renal and respiratory insufficiencies, redo surgery) was significantly higher in the CAVR group. 5) The intubation times, ICU- and hospital stay were significantly longer in the CAVR group. 6) The 30-day and 1-year mortality rates were significantly higher in the CAVR group.

After propensity score matching, the 2 subgroups were comparable in term of the preoperative characteristics. In comparison to CAVR our study shows that MIAVR is a safe and effective procedure associated with low incidence of postoperative mortality and good long-term survival rates, as well as a significant shorter ventilation time, a significant lower rate of blood transfusion, postoperative respiratory and renal insufficiency.

6. Summary of the Study

Background: CAVR via full sternotomy is a safe procedure providing excellent long-term outcomes (Bonacchi et al., 2002; Tabata et al., 2008; von Segesser et al., 1999). Over the past two decades, minimally access cardiac surgery has been increasingly adopted with the goal to reduce the invasiveness of surgical procedures and aiming in the same time to give the same quality, safety and results of the conventional surgery. In spite of that, randomized controlled trails as well as meta-analysis studies (Aris et al., 1999; J. M. Brown et al., 2009; Dogan et al., 2003; Murtuza et al., 2008), were not able to show a convincing superiority of MIAVR over CAVR

Aim: This study aimed to determine whether the MIAVR via upper partial sternotomy offers significant advantages in the postoperative outcomes (morbidities and mortalities) over CAVR via standard full sternotomy.

Patients and Methods: This study examined all patients who underwent first-time, isolated AVR at our institution during the period from January 2001 till Mai 2012. The data were collected from our database of 2416 patients and were evaluated for both procedures. After applying exclusion criteria, we analyzed and evaluated the outcomes of 2103 patients who underwent primary isolated AVR (CAVR, n=1167 and MIAVR, n=936). Due to differences in the preoperative baseline characteristics and to avoid any selection bias in both groups, data analysis was performed using a propensity score matching, where 585 patients were matched from each group.

Results: Before propensity matching, patients in the CAVR group were significantly older, included more females, and presented with significantly more comorbidities than those in the MIAVR group. Cardiopulmonary bypass and aortic cross clamp time were significantly longer in MIAVR than CAVR (94.8 ± 25 vs. 85.7 ± 27.1 min., and 67 ± 18.5 vs. 62 ± 19.7 min, $p < 0.001$, respectively). The amount of intraoperative autologous- and foreign blood transfusion were significantly lower in MIAVR group (940.2 ± 569.1 vs. 1033.5 ± 5538 ml and 257.9 ± 105.5 vs. 314.1 ± 170.3 ml, $p < 0.001$, respectively). Postoperative blood transfusions (autologous-, foreign blood, plasma and platelets) were also significantly lower in MIAVR**.** The incidence rates of Low cardiac output syndrome (1% vs. 2.3%, $p = 0.01$), postoperative arrhythmias (Atrial arrhythmias and AVB) (1.8% vs. 3.8% and 2.8% vs. 5.1%, $p = 0.002$, respectively), and the need for postoperative pacemaker implantation (2.7% vs. 5.3%, $p = 0.014$) were significantly lower in MIAVR group. Intubation times were significantly shorter in MIAVR (8 (6-13) vs. 9 (7-14) hours, $p=0.012$). The incidence of respiratory and renal insufficiencies (8.4 vs. 14.2% and 11.4vs. 16.8%,

***p*<0.001**, respectively) was also significantly lower in the MIAVR group. The incidence of cerebrovascular accident was also significantly lower in MIAVR group (1.6% vs. 4.1%, ***p*=0.03).** The ICU-and hospital stay was significantly shorter in MIAVR group (3 (2-5) vs. 5 (3-8) days and 9 (8-12) vs. 11 (8-14) days, ***p*<0.001**, respectively). The need for redo surgery was significantly lower in MIAVR (0.7% vs. 2.8%, ***p*<0.001).** Finally, 30-day, 1-year mortality rates were significantly lower in MIAVR (1.5% vs. 3.3%, ***p*<0.05** and 2.9% vs. 7.1%, ***p*<0.001,** respectively).

After performing propensity score matching the 2 subgroups were comparable in term of the preoperative characteristics. The mean age (65±10.5 vs. 65.7±11.5 years, *p*=0.23), and gender (females 37.2%, *p*=0.9) were similar in both subgroups. CPB times were still significantly longer in MIAVR than CAVR (93.5 ± 25 vs. 88 ± 28 min, ***p*<0.001**), but aortic cross-clamp times were similar in both subgroups (65.6 ± 18.4 vs. 64.3 ± 19.8 min, *p* = 0.25). Intraoperative and postoperative autologous-blood transfusions were still significantly lower in MIAVR subgroup (927.2 ± 425.6 vs. 1036.4 ± 599.6 ml, and 170.2 ±47.6 vs. 243.5 ± 89.3 ml, ***p* < 0.001,** respectively**)**. Intubation times were still significantly shorter in MIAVR (7 (5-11) vs. 8 (6-14) hours, ***p*=0.01**) The incidence of respiratory and renal insufficiencies was still significantly lower in the MIAVR subgroup (8.5 vs. 11.8%, ***p*=0.03,** and 9 vs. 16%, ***p* < 0.001,** respectively): Finally, there were no more significant differences between MIAVR and CAVR subgroups regarding to, postoperative foreign blood, plasma and platelets transfusions (*p*>0.05), the incidence of low cardiac output (*p*=0.14), the incidence of postoperative arrhythmias (*p*=0.38), the need for postoperative pacemaker implantation (*p*=0.17), the incidence of cerebrovascular accident (*p*=0.29), the ICU-and hospital stay (*p*=0.35, *p*=0.23, respectively) and the need for Redo surgery (*p*=0.14). Finally, the 30-day and 1-year mortality rates were similar in both subgroups (1.5% vs. 1.7%, *p*=0.74 and 3.1% vs. 4.8%, *p*=0.12, respectively).

Conclusion: Although, CPB times were on average 5 min longer in MIAVR, our institutional guidelines recommend this procedure for all patients who are going to have isolated AVR for the first time, as it is a safe procedure and associated with the same low incidence of mortality and good long-term survival as in CAVR. In addition, we found shorter intubation times, lower rates of postoperative renal and respiratory insufficiency and a lower amount of autologous blood transfusions in MIAVR when compared with CAVR.

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8. Appendix

8.1 Data used to generate the logistic regression model

Table 8.1. Preoperative variables used to generate the logistic regression propensity score

	Estimate	Standard error	Z- value	Pr(>|z|)
Intercept	0.964673	2.708184	0.356	0.7217
Age	0.053361	0.004564	11.692	< 2e-16
Sex (Female)	0.146254	0.136202	1.074	0.2829
Weight	0.014519	0.013751	1.056	0.2910
Height	-0.026513	0.014982	-1.770	0.0768
Preoperative serum creatinine	0.743265	0.175779	4.228	2.35e-05
Previous myocardial infarction	0.727912	0.520488	1.399	0.1620
LV-EF*	0.604566	0.110683	5.462	4.70e-08
Aortic valve pathology (Isolated AS)	-1.151560	0.993015	-1.160	0.2462

8.2 Supplementary results for patients before propensity matching (all patients)

Table 8.2. Supplementary results for all patients

	MIAVR	CAVR	*P*-value
All patients	**936**	**1167**	
Male, n (%)	614 (65.6)	620 (53.1)	**<0.001**
Weight (kg), mean ± SD	79.7 ± 14.6	77.6 ± 15.4	**<0.001**
Height (cm), mean ± SD	171.2 ± 9.3	168.7 ± 9.1	**<0.001**
Angina at Rest, n (%)	5 (0.5)	13 (1.1)	0.15
Instable angina, n (%)	3 (0.3)	9 (0.8)	0.17
Chronic restrictive pulmonary disease, n (%)	6 (0.6)	18 (1.5)	**0.05**
LV-EF*, mean ± SD	65.6 ± 17.8	65.3 ± 21.2	**0.02**
CPB cannulation			
Ascending aorta, n (%)	928 (99.1)	1149 (98.4)	0.94
Femoral artery, n (%)	8 (0.1)	18 (1.6)	0.16
Right atrium, n (%)	924 (98.7)	1153 (98.8)	0.97
Femoral vein, n (%)	12 (1.3)	14 (1.2)	0.97
Need for IABP (Intraoperative), n (%)	2 (0.2)	5 (0.4)	0.4
Conservative therapy for low CO*, n (%)	2 (0.2)	12 (1.0)	**0.01**
Conservative therapy for renal insufficiency, n (%)	76 (8.1)	126 (10.8)	**<0.001**
EuroSCORE-logistic, median (IQR)	3 (2-5)	6 (4-10)	**<0.001**
EuroSCORE-additive, median (IQR)	5 (3-6)	7 (5-8)	**<0.001**

8.3 Supplementary results for patients after propensity matching (matched patients)

Table 8.3. Supplementary results for patients after propensity matching

	MIAVR	CAVR	*P*-value
Propensity matched patients	**585**	**585**	
Male, n (%)	367 (62.8)	367 (62.8)	0.9
Weight (kg), mean ± SD	79.3 ± 13.9	79.5 ± 15.5	0.7
Height (cm), mean ± SD	170.5 ± 8.8	170.4 ± 9.1	0.8
Angina at Rest, n (%)	4 (0.7)	5 (0.9)	0.8
Instable angina, n (%)	3 (0.5)	3 (0.5)	0.9
Chronic restrictive pulmonary disease, n (%)	4 (0.7)	5 (0.9)	0.8
LV-Function, mean ± SD	64.6 ± 17.2	66.7 ± 21.3	0.09
CPB cannulation			
Ascending aorta, n (%)	577 (98.7)	580 (99.1)	0.59
Femoral artery, n (%)	8 (1.3)	5 (0.9)	0.59
Right atrium, n (%)	574 (98.1)	583 (99.7)	0.59
Femoral vein, n (%)	11 (1.9)	2 (0.3)	0.12
Need for IABP (Intraoperative), n (%)	2 (0.3)	3 (0.5)	0.24
Conservative therapy for low CO*, n (%)	2 (0.3)	5 (0.9)	0.28
Conservative therapy of renal insufficiency, n (%)	38 (6.5)	68 (11.6)	**< 0.001**

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