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List of abbreviations

AR = Aortic regurgitation

AVRR = Aortic valve and root replacement

AS = Aortic stenosis

ATAAD = Acute type A aortic dissection

AV = Aortic valve

BD = Bentall-De Bono

BR = Basal ring

CABG = Coronary artery bypass grafting

CAD = Coronary artery disease

COPD = Chronic obstructive pulmonary disease

CPB = cardiopulmonary bypass

CVG = Composite valve graft

DAPT = Dual antiplatelet therapy

DOAC = Direct oral anticoagulants

DM = Diabetes mellitus

ECC = Extracorporeal circulation

ECG = Electrocardiography

EF = Ejection fraction

FAA = Functional aortic annulus

ICU = Intensive care unit

IVSd = Diastolic interventricular septal wall thickness

LA = Left atrial

LV = Left ventricle

LVEDd = Left ventricular end-diastolic diameter

LVOT = Left ventricular outflow tract

MV = Mitral valve

STJ = Sino-tubular junction

TV = tricuspid valve

VAJ = Ventriculo-aortic junction

VSD = ventricular septal defect

1. Introduction

1.1 Background

Aortic valve and root replacement (AVRR) using a composite valve graft (CVG) as described by Bentall-De Bono (BD) is considered to be the gold standard in the treatment of aortic root pathologies with or without aortic valve (AV) disease.[2,3] It is mainly indicated to treat combined disease of the aortic valve and ascending aorta, including aneurysms or dissections of the ascending aorta associated with aortic valve stenosis, regurgitation and/or endocarditis. It is considered the treatment of choice when the aortic valve-sparing operation is not suitable and when the patients are not candidates for a Ross procedure.[4]

Since firstly described, the BD procedure using a prosthetic CVG has been widely performed and is reported to give generally favourable results. While the initial CVG contained a mechanical valve, nowadays the use of bioprosthetic valves dramatically increased over the past decades due to improved durability.[5] Development of surgical techniques has remarkably decreased the incidence of re-operation following aortic root pathologies, although major bleeding, thromboembolic complications and late mortality remain a concern.[2]

In this dissertation theses, a BD operation, its indications and application will be presented, however; the main aim is to analyse the short- and long-term results of this surgical procedure with particular regard to survival, freedom from reoperation, thromboembolic events and endocarditis.

1.2 History of aortic root replacement surgery

AVRR with CVG and reimplantation of coronary arteries is a standard procedure used in the management of various pathologies of the AV and aortic root.[6] The breakthrough in surgical approach for the replacement of the ascending aorta was first reported by Denton Cooley and Michael De Bakey, who performed the first successful surgical intervention for aneurysms involving the ascending aorta in 1956.[7] In the 1960s, with the introduction of CVG, it became possible to extend the therapeutic option to aortic root dilation with concomitant aortic regurgitation

(AR) by using CVG, when Hugh Bentall and Antony De Bono described their own technique in 1968, known later as the BD procedure.[8]

Although the BD procedure has remained a benchmark for treating aortic root pathologies, numerous modifications had been suggested by innovative surgeons over the last half of a century. The original procedures were improved, and other surgical techniques were developed to allow for more reliable and consistent operations.[8] Furthermore, in the 1980-90´s Sir Magdi Yacoub and Tirone David described their respective techniques of repairing the aortic root while focusing on sparing the native AV, thus providing their patients with freedom from a prosthetic valve related complications and consequently improved quality of life.[9,10] The basis of each of these techniques is the restoration of the anatomical structure of the aortic root.

1.3 Functional Anatomy

The aortic root is considered a complex anatomical structure, located in the middle of the heart and its components have connections to all cardiac chambers.[11] A thorough understanding of the anatomy of the aortic root and sinuses of Valsalva is essential for performing successful operations on the AV and the aortic root. The aortic root emerges from the aortic orifice, an opening from the left

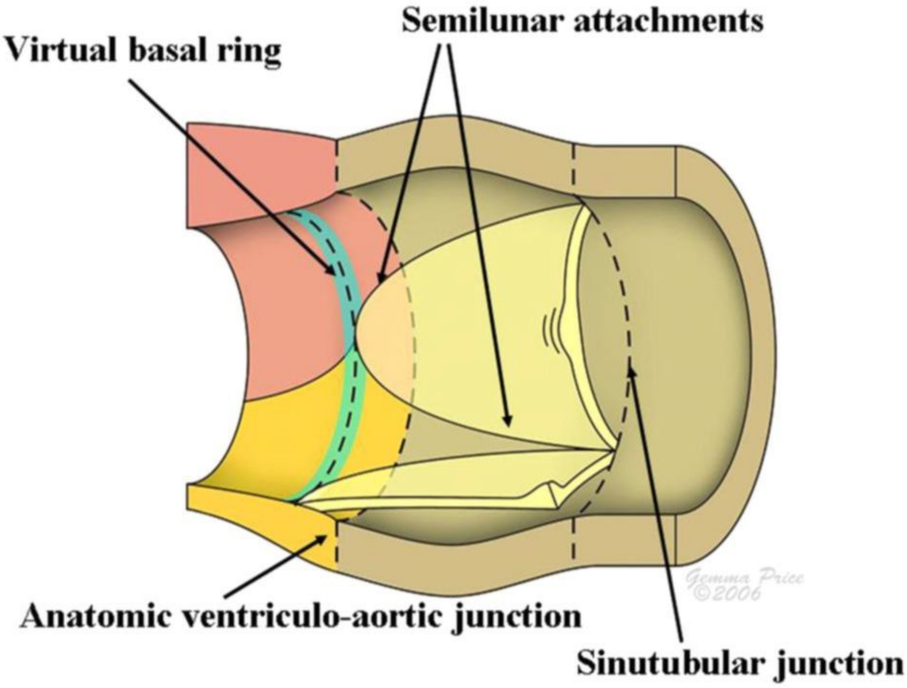

Figure 1. The cartoon shows a dissected aortic root, and illustrates how the semilunar attachment of the valvar leaflets incorporates aortic wall in the intersinusal triangles, and ventricular tissues at the base of each of the coronary aortic sinuses.[1]

ventricle and forms a bridge between the left ventricle and the systemic circulation through the ascending aorta. The term "aortic root" includes three structures: the functional aortic annulus (FAA), comprising of the ventriculo-aortic junction (VAJ) and the sinotubular junction (STJ); the leaflets and their attachment, and the three sinuses of Valsalva (Figure 1).[12] The aortic root extends from the basal attachment of the aortic cusps, or the virtual basal ring (BR), to their peripheral attachment at the level of the STJ.[13]

According to Anderson et al. the aortic root can be referred to as a complex structure consisting of several rings – 3 circular rings and 1 three-pointed-crown-like ring (Figure 2).[1] The STJ (blue ring) represents the top of the crown and is defined by the sinus ridge and the commissures of the cusps. It forms the outlet of the aortic root into the ascending aorta.[13] The VAJ represents a circular site (yellow

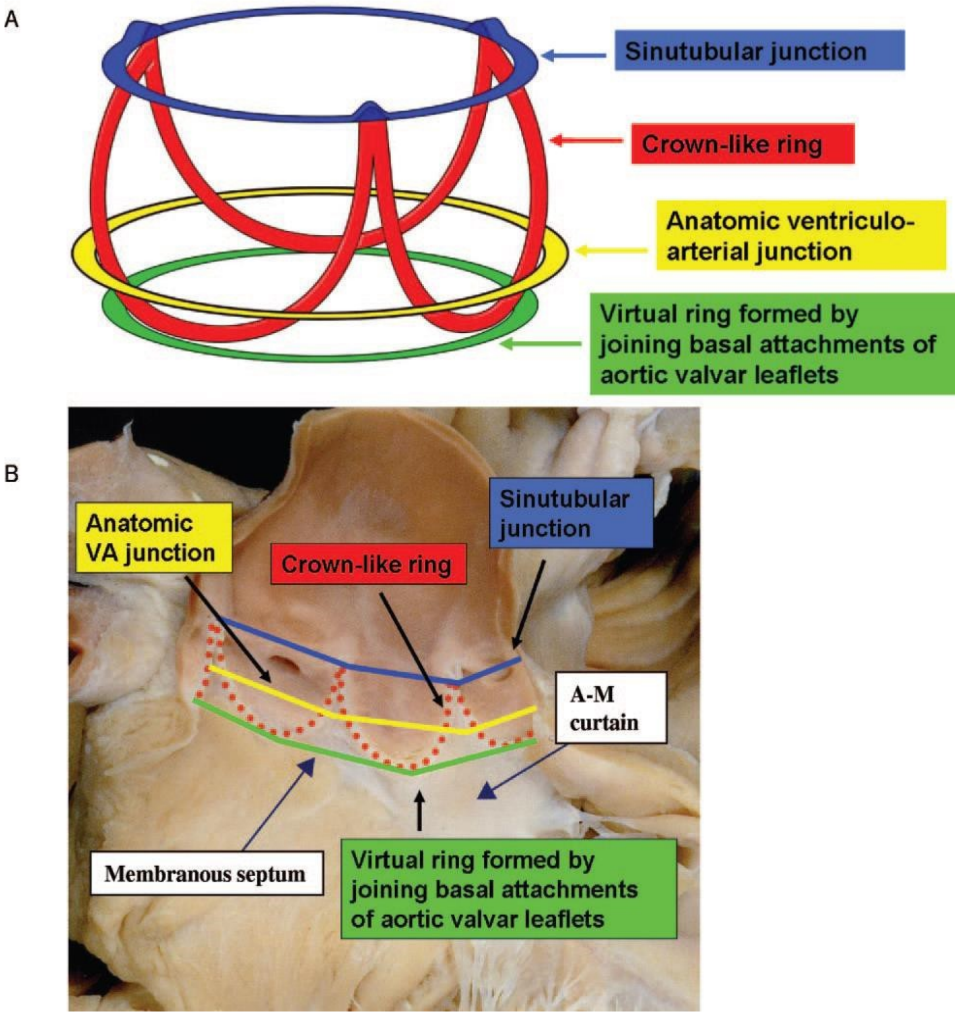

Figure 2. (A) Three-dimensional arrangement of the aortic root, which contains 3 circular "rings," but with the leaflets suspended within the root in crown-like fashion. (B) The leaflets have been removed from this specimen of the aortic root, showing the location of the 3 rings relative to the crown-like hinges of the leaflets. VA, ventriculo-aortic; A-M, aorto-mitral.[13]

ring) where the muscle tissue of the left ventricular outflow tract (LVOT) transitions into the fibroelastic wall of the sinuses of Valsalva. Approximately one half is composed of fibrous tissue and the other of muscular tissue. It is located across the lower third of the aortic cusps and represents a real anatomic region and thus is regarded as the anatomic VAJ.

The basal attachment points of the cusps form three semilunar lines. Because of their shape, each cusp is characterized by a nadir. The BR (green ring) is formed by joining the nadirs with an imaginary (virtual) ring. The BR represents the base of the crown and is located proximally to the VAJ. This plane corresponds to the functional aortic annulus as it represents the inlet from the LVOT into the aortic root and is often considered the echocardiographic aortic annulus.[11]

The aortic valve cusps take the form of a 3-pronged coronet (red line) and cross the VAJ at several points.[13] The place where the aortic cusps are attached to the aortic wall is referred to as the surgical aortic annulus as it represents the site where the sewing ring of the valve prosthesis, in case of replacement, is implanted.[11] The surgical annulus extends from BR to the STJ, formed by three commissures. It is sometimes called the haemodynamic junction, because it represents the boundaries between ventricular and aortic pressure.[11]

The aortic valve consists of cusps shaped like a three-pointed-crown-like structure in three-dimensional (3D) projection, and together they form a single functional unit.[14] The cusps form thin-walled pouch-like structures, appended to the wall of the aortic root and contain specialized tissue with fibrous, elastic, nervous, and muscular properties.[15] Anatomically these cusps can be divided into three parts: a free margin, a “belly”, and a basal or attachment part.[16] The free margin end of each cusp consists of slightly stronger tissue than the other parts. The centre of each free edge contains the fibrous nodulus Arantii, which divides the thin arc-shaped lunula on either side.[17]

As the valve opens, the cusps fall back into their sinuses without obstructing the coronary ostia. The semilunar attachments of cusps provide the AV its sealing ability and thus forming a hemodynamic junction between the left ventricle and the ascending aorta. All structures proximal to these attachments are subject to ventricular pressure, whereas all parts distal to the attachments are subjected to arterial pressure.[18]

The sinuses of Valsalva, also known as aortic sinuses, represent three anatomic bulges or dilatations of the aortic root that arise from the three closing cusps of the AV. They serve to optimize cusp-loading, improve transvalvular hemodynamics and reduce turbulence throughout the cardiac cycle.[7]

Two of the aortic sinuses give rise to the left and right coronary arteries, whereas the third sinus has no coronary artery and thus carries the name “non-coronary sinus”. As the walls of the sinus of Valsalva are considerably thinner than those of the aortic wall, surgical aortotomy is usually performed further away from this area.[19]

During the cardiac cycle, which can be divided into systole and diastole, the aortic root undergoes complex movements depending on changes in blood pressure and volume that aid opening and closing of the AV.

The ascending aorta is the vertical part of the thoracic aorta, which is the mobile segment of the aorta. It passes obliquely upward, forward, and to the right behind the sternum at a total length of about five centimetres.

1.4 Indications for treatment

The BD procedure has become a standardised operation for treating of a variety of aortic root and valve pathologies. Aortic aneurysms have been a growing problem in the general population, especially in patients with Marfan syndrome or other connective tissue disorders and remain the main indication for the Bentall-De Bono procedure. Although many patients remain asymptomatic, the risk of fatal consequences increases with growth of the aneurysm. Untreated annulo-aortic ectasia could lead to rupture with sudden death from cardiac tamponade with obstructive shock or acute dissection with acute AR and severe ischemia of the heart, brain and abdominal organs.[8] Other indications for the BD operation are considered AV disease, involving aortic stenosis (AS) or regurgitation (AR; or combination of both). Infectious endocarditis poses a great threat to the function of the AV and remains a potentially life-threatening disease, often requiring surgical intervention, as necrotic tissue must be excised, abscesses drained and all infectious material completely removed.[20] Some other congenital heart defects, such as subaortic stenosis and some forms of ventricular septal defects (VSD) are indicated for BD operation, especially since some are associated with AR.[21]

1.5 Surgical treatment

AVRR as described by Bentall and De Bono poses a real challenge due to its complexity. It involves the replacement of the ascending aorta, aortic root and AV with a CVG. For decades it has been the optimal surgical therapy for acute type A aortic dissection (ATAAD) or chronic aortic root aneurysm with accompanying dysfunction of the AV. Mechanical or biological prostheses are used on the CVG.[2]

The disadvantages of this operation when using mechanical valve prosthesis are the risk of thromboembolic complications, greater risk of bleeding due to the life-long anticoagulation therapy, endocarditis, limited hemodynamics of the valve substitutes, paravalvular leakage and lower quality of life. When using biological valves, although no life-long anticoagulation therapy is required, there is a particular risk of prosthetic valve degeneration due to their relatively poor durability compared to mechanical valves, with the need for reoperation or reintervention.[22]

Classically as described by BD in 1968, a full median sternotomy is performed under general anaesthesia. The pericardium is then opened, and retraction sutures are placed. A cardiopulmonary bypass is then established via cannulation of ascending aorta or aortic arch and right atrium using a two-stage cannula. The aorta is cross-clamped distal to the aneurysm and opened longitudinally. Cardioplegia is administered selectively into the coronary ostia. The ascending aorta is resected, and valve cusps are excised, along the surgical annulus in the three aortic sinuses. At this point the coronary arteries are detached from the aortic wall.[6] After sizing a CVG is selected and consequently sutured into the aortic annulus using either running or interrupted sutures (Figure 3). Then orifices are made to the side of the tubular prosthesis. The coronaries are then re-cannulated through the tube lumen and sutured to the wall of the prosthesis and thus reincorporated within the new aorta. After removing the coronary cannulas and evacuating air the distal anastomosis is then completed.[6]

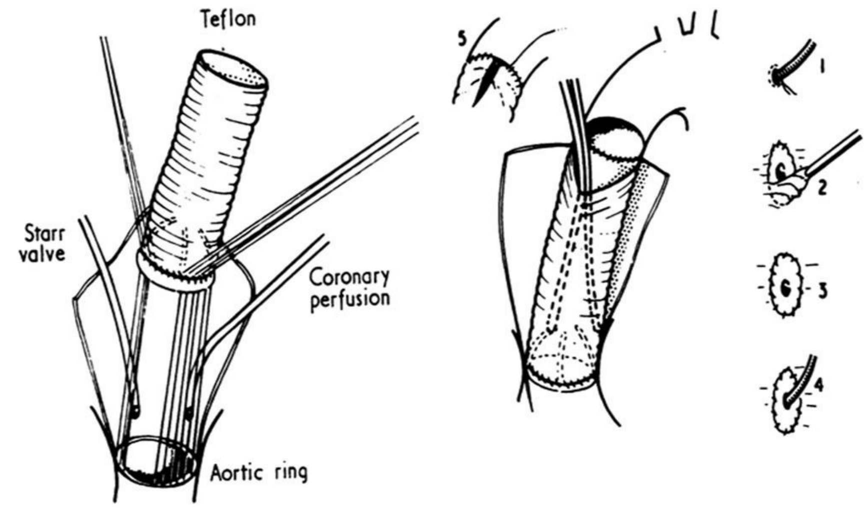

Figure 3. Classic drawing of Bentall's original root replacement.[6]

Over the time the frequency of these operations increased from isolated case reports to larger series. Longer postoperative observation revealed leaks occurring at the site of the coronary anastomosis with the CVG. These leaks were responsible for pseudoaneurysm formations at the coronary anastomosis, which grew to be a well-known concern following this original method.

The search for a solution to the problem of directly attaching the coronary arteries to the aortic prosthesis fuelled the next era of innovation and modifications to improve this technique, as well as the postoperative results and long-term outcom.[8] The changes to the original procedure consequently led to shorter intraoperative time, better haemostasis, and essentially decrease in the incidence and severeness of further complications. The main change provided by the modified version of the BD procedure, is in the degree of mobilization of coronary ostia. The initial BD procedure involves directly reimplanting the coronary arteries, while the modified technique requires the formation of ostial "button", thus avoiding complications linked to manipulating the ostia.[23] This technique was first described by Koustoubos et al. and involves the mobilization of the coronary arteries with a small cuff of surrounding aortic tissue (button).[24] An opening in the aortic prosthesis is then created using electrocautery. The anastomosis is then made by suturing these buttons in an end-to-side fashion with a running suture to the openings in the CVG[25] (Figure 4). The button modification to the original BD procedure has currently become the most widely used technique for AVRR.

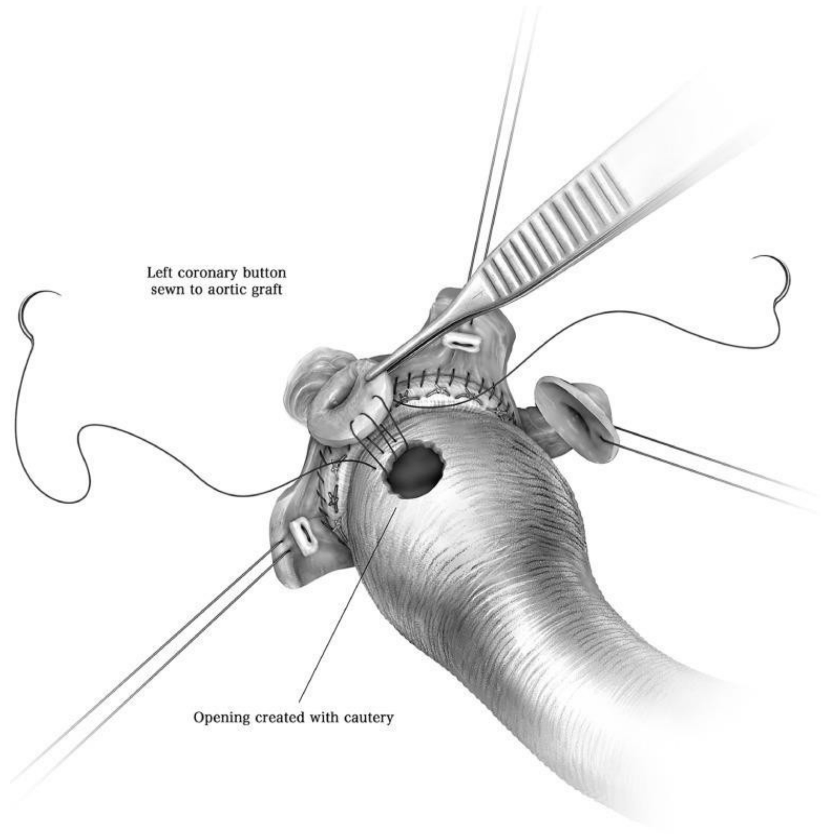

Figure 4. Anastomosis of the left coronary artery.[24]

This modification along with other techniques[26] dramatically reduced early complications and equipped surgeons with the necessary skillset to deal with any particular anatomy with the confidence of reaching a successful result of the operation. With the standardisation of the procedure the new aim was to discover a way to ensure long-term benefits of the operation. The procedure is now not only offered as an emergency or life-saving operation, but also as a pre-emptive means to prevent complications.[8] Rates of aortic root reoperation after the BD operation have decreased over the years. However, late mortality, major bleeding, and thromboembolic complications still remain a concern.[3]

A new operative access to the heart has also been implemented. Although providing the surgeon with enough space to operate, median sternotomy poses the threat of numerous postoperative complications such as wound dehiscence, sternal gapping, higher rate of infections, as well as increased scarring.[27] Minimally invasive surgery via “J“ or “T” shaped partial upper sternotomy also called “Mini-Bentall procedure” has become an alternative approach for aortic root replacement mainly for elective procedures. It has been reported to be a safe and less invasive option. Compared to the standard approach described by Bentall and

De Bono, it requires a slightly longer operative time, but proved to reduce post-operative morbidity and deliver a better postoperative outcome.[28]

1.6 Aim

The aim of this thesis was to evaluate the early- and long-term outcomes in patients undergoing AVRR with the BD operation. It should be stressed out that at our centre AV and root reconstructive techniques (David and Ross operations) are standard of care for patients with isolated AV and/or aortic pathologies, with fewer comorbidities and lower procedural risk. The patients with isolated AS receive Ross operation and patients with AR receive David operation. This implies that only severely diseased and high-risk patients with complex pathologies remain indicated for the BD procedure. We identified ATAAD and infective endocarditis, including majority of reoperations as leading complex pathologies. The differences in survival (early and late mortality), reoperation and complications (endocarditis, thromboembolism, graft dysfunction) were analysed in regard to the different indications (dissection, endocarditis, and other pathology) and to timing of the operation (emergent, urgent, and elective).

2. Material and Methods

2.1 Study design and patient selection

This is a single-centre retrospective study with prospective follow-up. After review of operative records 273 patients were identified, who underwent AVRR with CVG according to BD technique at the Goethe-University Hospital, Frankfurt/Main, Germany between 2005 and 2018. All patients who underwent AV-sparing root replacement, isolated AV replacement or AVRR with homograft were excluded from the study (Figure 5). Although aortic disease and some degree of AV dysfunction were present in all patients, we identified three major AV and/or aortic root pathologies as indication for the BD operation at our hospital: ATAAD, infective endocarditis and valve dysfunction (valve stenosis, regurgitation or combined disease). All 273 patients underwent an AVRR surgery with CVG (mechanical or biological). All preoperative data were retrieved from the aortic surgery database of the Goethe-University Hospital. The patients' medical records were reviewed to obtain data on patients´ demographics, symptoms, comorbidities, echocardiographic findings, previous surgical procedures, complications and survival rates. All patients received an echocardiographic examination and/or a CT scan prior to surgery depending on their condition upon hospital admission. The perioperative

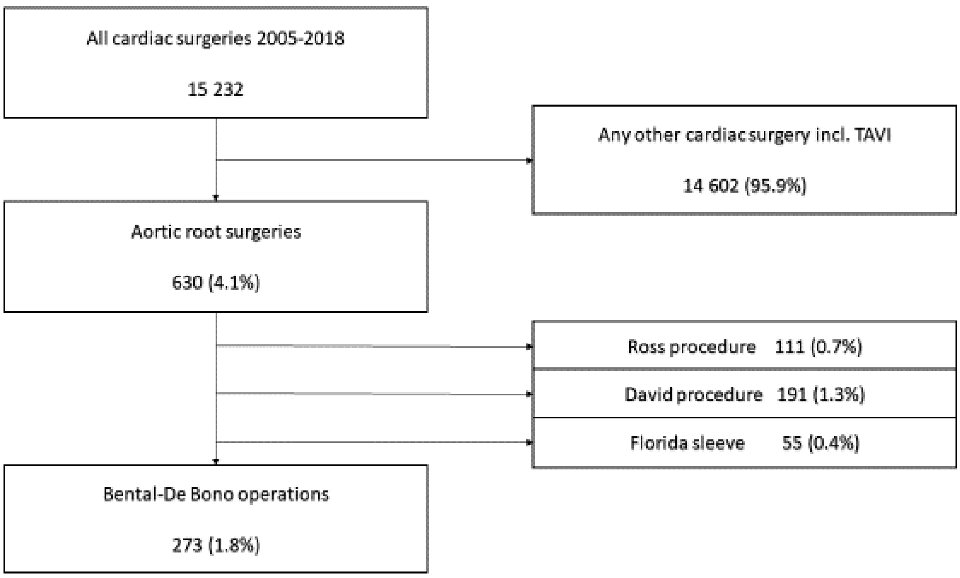

Figure 5. Flow-chart of the patient selection: operations between 2005-2018**.**

data were collected using the findings from the patient records and the electronic patient database. Intraoperative surgical data were acquired through operation protocols.

2.2 Echocardiography

The echocardiographic examination was carried out as either transthoracic or transoesophageal echocardiography and performed according to the recommendations of the German Society of Cardiology and the ACC/AHA/ASE guidelines for the assessment of the morphology and function of the AV and the left ventricular function and dimensions.[29] The morphology and function of the heart and valves were assessed in 2D and M mode. The valvular hemodynamics, including valve gradients were investigated using CW and colour Doppler. All data were digitally stored, evaluated and compared.

The assessment of pre- and postoperative AR was determined by transthoracic or transoesophageal echocardiography. The degree of AR was classified as follows: grade I (mild AR), grade II (moderate AR), grade III (moderately severe AR) and grade IV (severe AR).[21] The same applies for the classification of mitral valve (MV) and tricuspid valve (TV) regurgitation. The functional severity of pre- and postoperative AS was evaluated through measuring of pressure gradients and blood flow across the AV. Severe AS was defined as mean transaortic gradient ≥40 mmHg.[30]

The diameter of the ascending aorta as determined by computer tomography and echocardiography. Left ventricular pump function was classified by echocardiographic measurement as normal (ejection fraction (EF) ≥ 55%), mildly impaired (EF 45-55%), moderately impaired (EF 30-44%) or highly impaired (EF <30%). Other structural and dimensional parameters such as left ventricular end-diastolic diameter (LVEDd) or interventricular septal wall thickness also in diastole (IVSd) was also assessed.

The echocardiographic reference ranges for normal cardiac chamber size were determined as follows:

Table 1. Echocardiographic reference ranges.[31]

Parameters	Mean ± SD
IVSd (mm)	8.6 ± 1.6
LVEDd (mm)	44.3 ± 4.8
EF (%)	63.9 ± 4.9
AV mean gradient (mmHg)	<5
Ascending aortic diameter (mm) [32]	30.2 ± 4
AV, aortic valve; IVSd, diastolic interventricular septal wall thickness, LVEDd, left ventricular end-diastolic diameter; EF, ejection fraction	

The chamber quantitation protocols were approved by the European Association of Cardiovascular Imaging.

2.3 Baseline patient characteristics

Between May 2005 and December 2018, a total of 273 consecutive patients underwent AVRR using CVG at our institution. Two hundred eleven patients (77.3%) were male and 62 were female (22.7%). The mean patient age was 64.0 ± 12.8 years (range 22–89) The mean BMI was 26.9 kg/cm^2.

The patients were first divided into three different groups according to the pathology of the aortic root and to the indication for the surgery, respectively (Figure 6). Patients who suffered an ATAAD were included in the "Dissection" group (n = 48, 18%). The "Endocarditis" group (n = 99, 36%) included patients suffering from infectious endocarditis of the AV and/or aortic root. The third group or "All other

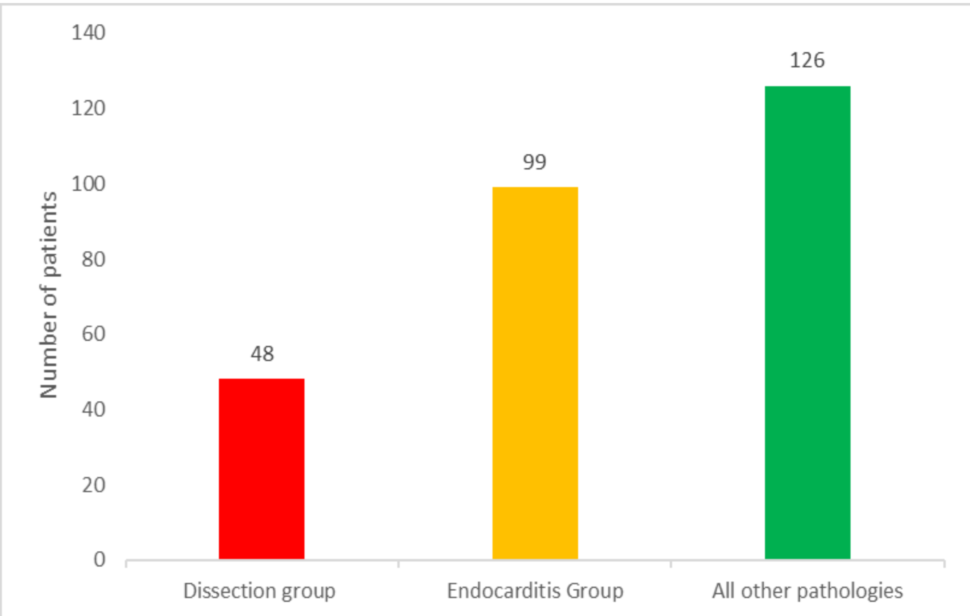

Figure 6. Distribution of patients´ groups according to leading pathology.

pathologies" (n = 126) consisted of patients, suffering from aortic valve/root pathologies, such as AV stenosis, regurgitation, a combination of both or significant aortic ectasia.

For better representation and visualization of the long-term analysis (survival, reoperation- and freedom from events), we decided to further divide our patients´ cohort: 1. according to the urgency of the operation (elective, urgent and emergency; Figure 7A) and 2. according to the type of the implanted prosthesis (biological and mechanical; Figure 7B). For simplification reasons this division was carried out only in regard to the Kaplan-Meier charts and not for the descriptive statistics.

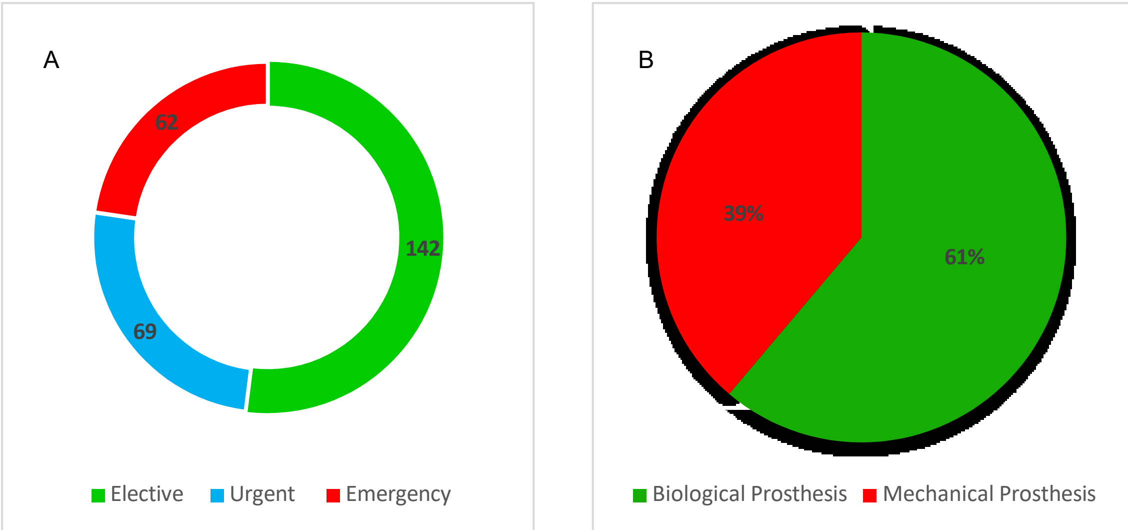

Figure 7. (A) Division of the patient cohort according to the urgency of operation. (B) Division of patient cohort according to the type of valve graft.

Patients suffering from ATAAD were significantly younger, taller and with the weight of 90kg pronounced heavier than those in other groups. Marfan's syndrome was present in 7 (2.2%) patients and, as expected, was more frequently observed among ATAAD patients. The endocarditis group was more often associated with previous cardiac surgery.

The cardiovascular functional status was assessed according to the New York Heart Association (NYHA) and results are summarised in Table 2. Patients from the endocarditis and other pathologies groups were categorized with significantly higher NYHA grades, than those in the dissection group. Ninety-eight (35.9%) patients suffered from cardiac failure upon hospitalization, 5 of whom were admitted with acute cardiogenic shock. Hypertension was present in 250 patients

(91.6%); coronary artery disease (CAD) was present in 101 patients (36.9%); 43 patients had diabetes mellitus (15.7%); and 105 have been previously diagnosed with pulmonary hypertension (38.5%). Ninety (32.9%) patients suffered from chronic obstructive pulmonary disease (COPD). Altogether the patients in the endocarditis and other pathologies groups were associated with more comorbidities than the ones in the dissection group.

Pre-operative electrocardiography (ECG) findings confirmed a sinus rhythm in 195 (71.4%) patients, whereas 59 (21.6%) patients were admitted with atrial fibrillations. Nineteen (7%) patients carried a previously implanted artificial cardiac pacemaker. There was a significant difference between the subgroups as almost all dissection patients (46/48) registered a sinus rhythm during the initial ECG upon admission, whereas patients from the other two groups showed more atrial fibrillations ($p = 0.006$).

One or more previous cardiac surgeries were performed in a total of 113 patients (41.4%). The following cardiac procedures were included in this category: AV repair and replacement, BD operation, Ross operation, David operation, MV repair and replacement, TV reconstruction, coronary artery bypass grafting (CABG), correction of aortic isthmus stenosis and of Fallot tetralogy. In detail: MV surgery (n = 8), TV surgery (n = 9), AV replacement (n = 97), aortocoronary bypass surgery (n = 26), Ross operation (n = 1), BD operation (n = 6), David operation (n = 6), supracoronary ascending aorta replacement (n=3), aortic arch replacement (n = 5), correction of tetralogy of Fallot (n = 1), aortic coarctation correction surgery (n = 2). The endocarditis group was more often associated with previous cardiac surgery than the other groups ($p < 0.001$).

There was a significant difference between the groups as 34 out of the 50 patients suffering from a previous neurologic condition were from the endocarditis group, representing a common accompanying symptom of the disease ($p < 0.001$).

The AV was congenitally bicuspid in 70 patients (25.6%) and 1 patient (0.4%) had a congenital unicuspidal AV, whereas the remaining 202 patients (74%) had a tricuspid aortic valve. The other pathologies group had the most patients with a congenital bicuspid aortic valve ($p < 0.001$). The full baseline characteristics of all 273 patients are listed in Table 2.

Table 2. Demographic data of entire patient´s cohort and according to 3 subgroups.

Variable	Overall (n=273)	Dissection Group (n=48)	Endocarditis Group (n=99)	All other pathologies (n=126)	p-value
Age (mean) in years + SD	64 ± 12.8	54.8 ± 14.5	65.8 ± 12.8	66.2 ± 10.4	<0.001
Male	211 (77.3%)	36 (75%)	77 (78%)	98 (78%)	
Female	62 (22.7%)	12 (25%)	22 (22%)	28 (22%)	0.92
Height (cm) mean	174.4	179	173	174	0.003
Weight (kg) mean	82.7	90	80	82	0.013
NYHA					<0.001
Grade I	25 (9.2%)	11 (23%)	3 (3%)	11 (9%)	
Grade II	77 (28.2%)	11 (23%)	23 (23%)	43 (34%)	
Grade III	112 (41%)	8 (17%)	50 (50%)	54 (42%)	
Grade IV	59 (21.6%)	18 (38%)	23 (23%)	18 (14%)	
Pre-operative ECG					0.006
Sinus rhythm	195 (71.4%)	46 (96%)	63 (63%)	86 (68%)	
Atrial fibrillation	59 (21.6%)	0	30 (30%)	29 (23%)	
Pacemaker rhythm	19 (7%)	2 (4%)	6 (6%)	11 (9%)	
Previous cardiac surgery	113 (41.4%)	2 (4%)	79 (80%)	32 (25%)	<0.001
CAD	101 (36.9%)	9 (19%)	41 (41%)	51 (40%)	0.017
Hypertension	250 (91.6%)	39 (81%)	88 (89%)	123 (98%)	0.001
Pulmonary Hypertension	105 (38.5%)	3 (6%)	48 (48%)	54 (43%)	<0.001
Heart failure upon admission	98 (35.9%)	12 (25%)	50 (51%)	36 (29%)	0.001
Carotid disease	17 (6.2%)	3 (6%)	5 (5%)	9 (7%)	0.81
PAD	16 (5.8%)	3 (6%)	8 (8%)	5 (4%)	0.42
Diabetes	43 (15.7%)	6 (13%)	21 (21%)	16 (13%)	0.174
COPD	90 (32.9%)	4 (8%)	38 (38%)	48 (38%)	<0.001
Previous Neurologic disorder	50 (18.3%)	5 (10%)	34 (34%)	11 (9%)	<0.001
Renal insufficiency	97 (35.5%)	15 (31%)	43 (43%)	39 (31%)	0.12
Marfan's syndrome	7 (2.2%)	4 (8%)	1 (1%)	2 (2%)	0.02
Native aortic valve					<0.001
Unicuspid	1 (0.4%)	0	0	1 (1%)	
Bicuspid	70 (25.6%)	11 (23%)	9 (9%)	50 (40%)	
Tricuspid	202 (74%)	37 (77%)	90 (91%)	75 (60%)	

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; ECG, electrocardiography; PAD, peripheral artery disease; SD, standard deviation

2.3.1 Preoperative Echocardiography

Upon hospital admission most of the patients received a preoperative echocardiography examination to determine the severity of their pathology. LVEDd, IVSd, EF, AV mean gradients, as well as the diameter of the ascending aorta were all significantly increased compared to the reference ranges for normal cardiac parameters as suggested in Table 1. AR was found in 194 patients (71.1%) with most patients suffering from a grade III AR (41.2% of 194 patients). MV regurgitation was present in 158 patients (57.9%), whereas 132 patients (48.3) suffered from TV regurgitation. Furthermore, preoperative echocardiogram showed significantly wider diameter of the ascending aorta among patients operated due to ATAAD. Both the "endocarditis" and the "other pathologies" group, on the other hand, were more associated with valve pathologies such a MV and TV insufficiency of mild and intermediate grade (Grade I and II). Detailed summary of the preoperative echocardiography is provided in Table 3.

Table 3. Preoperative echocardiography data.

Variable	Overall (n=273)	Dissection Group (n=48)	Endocarditis Group (n=99)	All other pathologies (n=126)	p-value
LVEDd (mm)	54.19	52.82	53.75	54.62	0.98
IVSd (mm)	13.78	12.38	13.49	14.08	0.44
EF (%)	56.428	58.41	55.894	56.53	0.96
AV gradient max (mmHg)	38.88	33.00	31.50	44.02	0.50
AV gradient mean (mmHg)	24.49	17.15	20.06	27.87	0.90
Ascending aortic diameter (mm)	44.09	56.58	35.56	47.00	<0.001
AR (overall)	194 (71.1%)				0.002
Grade I	50 (18.3%)	3 (6%)	24 (24%)	23 (18%)	
Grade II	53 (19.4%)	4 (8%)	14 (14%)	35 (25%)	
Grade III	80 (29.3%)	17 (35%)	28 (28%)	35 (25%)	
Grade IV	11 (4%)	4 (8%)	3 (3%)	4 (3%)	
MV regurgitation (overall)	158 (57.9%)				0.65
Grade I	97 (35.5%)	5 (10%)	43 (43%)	49 (39%)	
Grade II	45 (16.5%)	2 (4%)	23 (23%)	20 (16%)	
Grade III	14 (5.2%)	0	7 (7%)	7 (6%)	
Grade IV	2 (0.7%)	0	1 (1%)	1 (0.8%)	

TV regurgitation (overall)	132 (48.3%)				0.59
Grade I	99 (36.3%)	3 (6%)	46 (46%)	50 (40%)	
Grade II	29 (10.6%)	2 (4%)	10 (10%)	17 (13%)	
Grade III	4 (1.5%)	0	3 (3%)	1 (0.8%)	
Grade IV	0	0	0	0	
AR, aortic regurgitation; AV, aortic valve; EF, ejection fraction; IVSd, diastolic interventricular septal wall thickness, LVEDd, left ventricular end-diastolic diameter; MV, mitral valve; TV, tricuspid valve					

2.4 Surgical technique

The following procedure has been standardised in our Department. Depending on comorbidities and other functional heart conditions the approach and concomitant interventions may vary. Two hundred and twenty-five patients were operated through complete median sternotomy. Forty-eight patients (17.6 %) underwent a partial upper ministernotomy as previously reported.

The operation begins with a team time-out and a review of the operative checklist. Perioperative antibiotic prophylaxis is administered prior to skin incision. In patients suffering from endocarditis the preoperative antibiotics are being continued. After skin disinfection and sterile draping, the sternal incision and median sternotomy are performed in standard fashion. The anterior mediastinum is then exposed and carefully examined. The pericardium is opened, and pericardial sutures are placed. Now the heart dimensions and pump function, as well as the ascending aorta are visually evaluated. Venous cannulation of the right atrial appendage with two stage cannula or bicaval cannulation of the superior and inferior vena cava is then completed. A standard arterial cannulation was performed either through the distal aortic arch or right axillary, which ensures the start of the extracorporeal circulation (ECC). Once cardiopulmonary bypass is established, systemic cooling is started immediately, followed by aortic cross-clamping and a transverse aortotomy. Blood cold cardioplegic solution (Calafiore) was infused directly into the coronary ostia to protect the heart. After sizing the aortic annulus, the composite graft was implanted with a series of pledgeted everted sutures with 2-0 Ticron. We employed the ‘Button technique’ for coronary reimplantation in all patients. Then, the distal ascending aorta was transected and anastomosed to the CG with continuous 3/0 or 4/0 Prolene suture and in some cases reinforced by a strip of Teflon felt placed outside of the aorta. In cases, the intervention at the aortic arch and deep hypothermic circulatory arrest was needed, for the brain protection we applied an antegrade bilateral selective cerebral perfusion via the left axillary artery (with brachiocephalic trunk clamped) and left carotid artery. Provided that the anastomosis is intact the aortic clamp was removed and de-airing via aortic root cannula was completed. ECC was gradually reduced and the extracorporeal perfusion was terminated with the decannulation of the aortic root cannula. After careful haemostasis drains were placed and the pericardium was closed. The sternum was closed with wires, followed by a layered wound closure and intracutaneous skin suture.

2.5 Follow-up

The main endpoints of the study were defined as all-cause mortality, AV- or aortic root-related reoperation, as well as adverse valve-related events, such as structural or non-structural prothesis dysfunction, bleeding, embolism or prosthetic valve endocarditis. Follow-up information was gathered from the date of the surgery to the earlier of either date of death or the last contact to the alive patient. The follow-up process was terminated in November 2020. Follow-up data about patient’s physical condition (assessed by NYHA class), postoperative events (reoperation, haemorrhage, endocarditis, thrombo-embolic event) were collected using operation-specific questionnaires, which were send to every patient per post. Causes of death were obtained from records in the patient files or the in-house database. Missing data were supplemented by telephone interviews with the patients. Clinical, ECG and echocardiographic findings, as well as information concerning comorbidities and current medication were obtained from the referring general practitioners or cardiologist by letter and/or telephone call. Follow-up was completed in 96.3% of patients. The mean follow-up was 8.6 years (range 0–15.7 years), corresponding to a total of 1450 patient-years.

2.6 Statistical Methods

All data available were collected retrospectively and entered in an Excel® (Microsoft Corp, Redmond, Wash) spreadsheet. Categorical variables were presented as numbers and percentages; continuous variables were presented as mean and standard deviation. For the calculation of the p-values to compare individual surgical techniques, the Fischer’s exact test was used for the qualitative variables and the Kruskal-Wallis test for the quantitative variables. The distribution of a time-to-event outcome and event-free period were estimated using Kaplan-Meier curves and the comparison between the groups was performed using log-rank test. Univariate and multivariate logistic regression analysis of predictors for mortality was performed to evaluate the association between independent risk factors, comorbidities and mortality. Multivariate Cox regression identified the independent risk factors of long-term mortality after Bentall-De Bono procedure. A p-value of <0.05 was considered as statistically significant. The statistical calculations were carried out with the help of the SPSS 21.0 Statistical software for Windows (SPSS, Chicago, IL, USA).

2.7 Ethical aspects and data protection

The study was approved by the local Ethic Committee of the University Hospital Frankfurt (Reference number: 154/18; first approval date: 19 July 2013; most recent approval date: 10 June 2020), and an informed consent was obtained from each patient.

3. Results

3.1 Intraoperative results

The AVRR was performed as an emergency in 62 patients (22.7%), as an urgent procedure (no discharge between indication to surgery and operation) in 69 patients (25.3%), and electively in 142 patients (52%). As presumed, among the patients operated due to ATAAD the surgery was performed significantly more often in the emergent mode, the mechanical conduit was preferred and complete sternotomy was used ($p < 0.001$). In our study 167 patients (61.2%) received a biological CVG, whereas 106 patients (38.8%) were subject to a mechanical CVG. The decision whether to use a mechanical or biologic prosthesis was made on an individual basis by the surgeon and the patient. A full sternotomy was performed in 225 (82.4%) patients, whereas 48 (17.6%) were operated in minimally invasive technique.

In 97 (35.5%) patients one or more concomitant procedures were performed. Coronary artery bypass grafting surgery was performed in 62 patients (22.7%), MV surgery (replacement or reconstruction) in 32 patients (11.7%), and TV surgery (only reconstruction) in 26 patients (9.5%). Aortic arch surgery (total or partial arch replacement) was performed in 13 patients (4.8%). The number of bypass operations refers not only to the patients who had CAD, but also to patients who were diagnosed with coronary artery pathology due to ATAAD. The BD procedure was performed as a redo surgery in 109 (39.9%) patients. Patients from the “all other pathologies” group were significantly more likely to receive concomitant surgery ($p < 0.001$)

The median cardio-pulmonary bypass (CPB) time was 193 (477-60) minutes in the overall cohort. In the “dissection” group it was 213 (477-106) minutes, 211 (431-107) minutes in the “endocarditis” group and 173 (439-60) minutes in the “all other pathologies” group, respectively. The median aortic cross-clamp time was 131 (374-47) minutes in the overall cohort. For “dissection” patients it was 137 (374-69) minutes, 140 (239-71) for “endocarditis” and 122 (253-47) minutes for “all other pathologies”, respectively. Further operative characteristics are listed in Table 4.

Table 4. Operative data.

Variable	Overall (n=273)	Dissection Group (n=48)	Endocarditis Group (n=99)	All other pathologies (n=126)	p-value
Timing of operation					<0.001
Emergent	62 (22.7%)	44 (92%)	15 (15%)	3 (2%)	
Urgent	69 (25.3%)	2 (4%)	45 (46%)	22 (18%)	
Elective	142 (52%)	2 (4%)	39 (39%)	101 (80%)	
AV prosthesis					<0.001
Biological	167 (61.2%)	14 (29%)	78 (79%)	75 (60%)	
Mechanical	106 (38.8%)	34 (71%)	21 (21%)	51 (40%)	
Conduit diameter (mm)	25.1	25.5	24.6	25.4	0.05
Concomitant surgery					<0.001
CABG	62 (22.7%)	10 (21%)	14 (14%)	38 (30%)	
MV replacement	6 (2.2%)	0	3 (3%)	3 (2%)	
MV reconstruction	26 (9.5%)	0	12 (12%)	14 (11%)	
TV reconstruction	26 (9.5%)	0	8 (8%)	18 (14%)	
Operative access					<0.001
Complete sternotomy	225 (82.4%)	46 (96%)	89 (90%)	90 (71%)	
Minimally invasive	48 (17.6%)	2 (4%)	10 (10%)	36 (29%)	
CPB time, median (range), minutes	193 (477-60)	213 (477-106)	211 (431-107)	173 (439-60)	0.58
Cross-clamp time, median (range), minutes	131 (374-47)	137 (374-69)	140 (239-71)	122 (253-47)	0.72
Intraoperative complications (bleeding, second pump, low output, coronary problem or other)	40 (14.6%)	13 (27%)	19 (19%)	8 (6%)	0.49

AV, aortic valve; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; MV, mitral valve; TV, tricuspid valve

3.2 Early postoperative outcomes

The operative mortality was 0.7%. The overall early mortality until the postoperative day 30 amounted to 17.2% (47 of 273 patients), with significant differences between patients who received a biological valve graft and those with a mechanical CVG (83% [39/47 patients] vs 17% [8/47] respectively; $p < 0.001$). The 30-day mortality rate of “endocarditis” patients was also significantly higher than those of patients from the “dissection” and “other pathologies” groups ($p = 0.004$).

Causes of death were multiple organ dysfunction syndrome in 13, low cardiac output syndrome in 12, bleeding in 11, sepsis in 7 and cerebrovascular accident in 4 patients.

Fifty-five (20.1%) patients had re-exploration due to bleeding and/or cardiac tamponade. Early postoperatively, 13 patients (4.7%) suffered from any neurologic disorder such as major and minor stroke or transient ischemic attacks with only temporary neurologic dysfunction. Sixty-eight patients (24.9%) suffered from renal failure and needed postoperative dialysis, with the majority of the patients belonging to the “endocarditis” Group” (p < 0.001). Seven patients (2.6%) suffered from a myocardial infarction postoperatively, with 2 of them dying in the hospital. Another cardiac complication was heart block requiring a pacemaker implantation. This occurred in 8.8% (24 patients) of our population. Pericardial effusion also occurred as a common in-hospital complication and was found in 59 patients (21.6%), resulting in 53 cases into the immediate surgical intervention or a percutaneous CT-controlled drainage.

Table 5. In-hospital outcomes.

Variable	Overall (n=273)	Dissection Group (n=48)	Endocarditis Group (n=99)	All other pathologies (n=126)	p-value
Re-exploration for bleeding	55 (20.1%)	9 (19%)	22 (22%)	24 (19%)	0.81
Neurology	13 (4,7%)	3 (6%)	6 (6%)	1 (0.8%)	0.003
Renal failure (dialysis)	68 (24.9%)	11 (23%)	39 (40%)	18 (14%)	<0.001
Pacemaker	24 (8.8%)	7 (15%)	11 (11%)	6 (5%)	0.07
Myocardial infarction	7 (2.6%)	1 (2%)	3 (3%)	3 (2%)	0.93
Pericardial effusion	59 (21.6%)	9 (19%)	27 (27%)	23 (18%)	0.81
Wound healing disorder	20 (7.3%)	2 (4%)	9 (9%)	9 (7%)	0.62
ECG-rhythm at discharge					
Sinus rhythm	160 (58.6%)	31 (65%)	47 (47%)	82 (65%)	0.002
Atrial fibrillation	39 (14.3%)	1 (2%)	14 (14%)	24 (19%)	
Pacemaker rhythm	39 (14.3%)	9 (19%)	17 (17%)	13 (10%)	
30-day mortality	47 (17.2%)	9 (19%)	26 (26%)	12 (10%)	0.004

ECG, electrocardiography

3.2.1 Postoperative (discharge) echocardiography

Postoperative LVEDd significantly decreased from 54.2 ± 9.4 mm to 51.6 ± 6.7mm ($p < 0.001$). The IVSd also dropped from a mean of 13.8 ± 3.0 mm to 13.3 ± 2.4mm ($p < 0.001$). The AV peak and mean gradients declined (38.9 ± 2.1mmHg to 23.1 ± 0.9mmHg and 24.5 ± 1.4 to 13.7 ± 0.6mmHg respectively). All patients subject to postoperative Echocardiography showed either no remaining AR or Grade I AV prosthesis regurgitation (8.8%), which depicts a substantial improvement of AV function. The number of MR and TR also declined after procedure. The ascending aorta measured at a mean of 27.94 ± 4.1mm, which showed a significant difference ($p < 0.001$) from the preoperative measurements (44.1 ± 13.9mm). The full summary of the discharge echocardiographic examination can be found in Table 6.

Table 6. Discharge echocardiography data.

Variable	Overall (n=273)	Dissection Group (n=48)	Endocarditis Group (n=99)	All other pathologies (n=126)	p-value
LVEDd (mm)	51.61	50.75	50.28	52.56	0.37
IVSd (mm)	13.33	13.53	12.86	13.60	0.17
EF (%)	54.22	58.07	53.81	53.42	0.74
AV-Gradient max (mmHg)	23.15	23.60	26.23	21.04	0.11
AV-Gradient mean (mmHg)	13.67	14.84	15.27	12.34	0.16
AV-area (cm^2)	1.92	2.09	1.89	1.92	0.31
AR					0.56
Grade I	24 (8.8%)	3 (6%)	6 (6%)	15 (12%)	
Grade II	0	0	0	0	
Grade III	0	0	0	0	
Grade IV	0	0	0	0	
MV regurgitation					0.38
Grade I	92 (33.7%)	13 (27%)	38 (38%)	41 (33%)	
Grade II	19 (6.9%)	2 (4%)	6 (6%)	11 (9%)	
Grade III	0	0	0	0	
Grade IV	0	0	0	0	
TV regurgitation					0.38
Grade I	90 (33%)	11 (23%)	37 (37%)	42 (33%)	
Grade II	10 (3.7%)	2 (4%)	2 (2%)	6 (5%)	
Grade III	0	0	0	0	
Grade IV	0	0	0	0	
Ascending aortic diameter (mm)	27.94	26.91	27.49	28.63	0.14

AR, aortic regurgitation; AV, aortic valve; EF, ejection fraction; IVSd, diastolic interventricular septal wall thickness, LVEDd, left ventricular end-diastolic diameter; MV, mitral valve; TV, tricuspid valve

3.3 Long-term results

Of all hospital survivors (143 patients), 133 (93%) were available and 10 were lost to follow-up. The mean follow-up time was 102.9 ± 5.2 months (range 1-188 months). Eighty-three patients (30%) died during the follow-up. During the follow-up period only 3 confirmed cardiac-related deaths. This number resulted from a lack of sufficient information about the cause of death of 62 of the 83 patients. Other known causes of death are cancer, multiple organ failure, infectious diseases and cerebrovascular accidents. Of the 133 alive patients contacted, only 16 patients (12%) or next of kin reported some kind of complication during the follow-up period. Endocarditis and thrombo-embolisms were the most frequent late complications after AVRR. Eight patients (6%) reported a major adverse cardiovascular and cerebral event - either a stroke, myocardial infarction or an embolic closure of the renal artery. Eight patients (6%) suffered from endocarditis at some stage in the follow-up period and all of them had to be reoperated on the CVG. One hundred and thirty patients (97.7%) were subject to regular intake of anticoagulants, with almost three fourths of them (76%) taking coumadin. The follow-up NYHA functional class improved significantly (2.75 ± 0.89 to 1.76 ± 0.79; $p < 0.001$). Regarding the final outcome after surgical intervention the vast majority of patients (88.8%) followed the path to complete recovery and reported a satisfactory result from the operation. Only 11 (8.2%) of the surviving patients required a reoperation during the follow up period. The most common reason for the reoperation was endocarditis (8/11), followed by valve dysfunction (2/11) and pseudoaneurysm of the CVG.

Table 7. Long-term results.

Variable	Overall alive patients (n=133)	Dissection Group (n=26)	Endocarditis Group (n=42)	All other pathologies (n=65)	p-value
NYHA					
Grade I	58 (43.6%)	11 (42%)	22 (16.5%)	25 (18.8%)	0.17
Grade II	53 (39.8%)	8 (31%)	17 (12.8%)	28 (21%)	
Grade III	18 (13.5%)	7 (27%)	2 (1.5%)	9 (6.8%)	
Grade IV	4 (3%)	0	2 (1.5%)	2 (1.5%)	
Complications	16 (12%)	3 (12%)	3 (2.2%)	10 (7.5%)	0.49
Thromboembolism	8 (6%)	2 (8%)	0	6 (4.5%)	0.23
Endocarditis	8 (6%)	1 (4%)	2 (1.5%)	5 (3.8%)	0.11

AV Dysfunction	4 (3%)	0	0	4 (3%)	0.09
Anticoagulants	130 (97.7%)				
Coumadin	76 (57.1%)	20 (77%)	23 (17.3%)	33 (24.8%)	
ASA	31 (23.3%)	3 (12%)	9 (6.8%)	19 (14.3%)	0.26
DOACs	20 (15%)	2 (8%)	9 (6.8%)	9 (6.8%)	
DAPT	3 (2.2%)	0	1 (0.7%)	2 (1.5%)	
Outcome					
Restitution	118 (88.8%)	23 (88%)	39 (29.3%)	56 (42.1%)	0.66
Re-Operation	11 (8.2%)	3 (12%)	3 (2.2%)	5 (3.8%)	
Permanent deficit	3 (2.2%)	1 (4%)	0	2 (1.5%)	
ECG-rhythm					
Sinus rhythm	81 (60.9%)	18 (69%)	23 (55%)	40 (62%)	
Atrial fibrillation	22 (16.5%)	2 (8%)	12 (29%)	12 (18%)	0.56
Pacemaker rhythm	30 (22.6%)	6 (23%)	12 (29%)	15 (23%)	

ASS, acetylsalicylic acid; AV, aortic valve; DAPT, dual antiplatelet therapy DOACs, direct oral anticoagulants; ECG, electrocardiography,

3.3.1 Late survival

One hundred and thirty patients (47.6%) died during the follow-up. Overall, follow-up mortality rate was 47.6% (130 patients) with significantly better results of the dissection group. On the contrary, the patients operated due to infective endocarditis proved the lowest long-term survival rate ($p = 0.008$). Detailed late survival data are presented in in Table 9.

Table 8. Survival data.

Variable	Overall (n=273)	Dissection Group (n=48)	Endocarditis Group (n=99)	All other pathologies (n=126)
Patients alive	133 (48.7%)	26 (54%)	42 (42%)	65 (52%)
Deaths	130 (47.6%)	18 (38%)	54 (55%)	58 (46%)
Mortality rate	47.6%	37.5%	54.5%	46%
Lost to Follow-up	10 (3.7%)	4 (8%)	3 (3%)	3 (2%)

Various factors were analysed for impact on the mortality. In univariate analysis, age (OR 1.052, 95% CI 1.028-1.075, $p<0.01$), NYHA (OR 1.42, 95% CI 1.076-1.876, $p = 0.013$), previous surgery (OR 1.636, 95%CI 0.955-2.558, $p = 0.006$), CAD (OR 1.58, 95%CI 0.958-2.618, $p<0.05$), diabetes (OR 2.65, 95%CI 1.309-5.368, $p = 0.007$), renal insufficiency (OR 2.57, 95%CI 1.530-4.330, $p < 0.05$), peripheral artery disease (OR 4.4, 95%CI 1.214-16.000, $p = 0.024$), biological CVG (OR 1.99, 95%CI 1.196-3.312, $p=0.008$), concomitant surgery (OR: 1.633, 95% CI 0.998-2.672, p = 0.03), postoperative re-exploration for bleeding (OR: 3.37, 95% CI 1.751-6.429, p < 0.01), postoperative neurologic dysfunction (OR 5.45, 95%CI 1.172-25.416, p = 0.031) and postoperative renal replacement therapy (OR 3.09, 95% CI 1.705-5.616, p < 0.01) were identified as independent predictors of mortality (Table 10).

Table 9. Predictors of mortality in an univariate logistic regression analysis.

Variables	Patients (n=273)		
	OR	95% CI	p-value
Age	1.052	1.028-1.075	<0.001
NYHA	1.42	1.076-1.876	0.013
Previous cardiac surgery	1.636	0.955-2.558	0.006
Diabetes	2.65	1.309-5.368	0.007
Coronary artery disease	1.58	0.958-2.618	<0.05
Renal insufficiency	2.57	1.530-4.330	<0.05
Peripheral artery disease	4.4	1.214-16.000	0.024
Biological valve graft	1.99	1.196-3.312	0.008
Concomitant surgery	1.633	0.998-2.672	0.03
Re-exploration for bleeding	3.37	1.751-6.429	<0.001
Postoperative neurologic dysfunction	5.45	1.172-25.416	0.031
Postoperative renal replacement therapy	3.09	1.705-5.616	<0.001

In a multivariate Cox regression analysis, age (OR 1.046, 95% CI 1.022-1.070, p<0.01), pulmonary hypertension (OR 1.810, 95%CI 1.159-2.825, p = 0.009), preoperative ECG rhythm (OR 1.726, 95%CI 1.066-2.795, p = 0.026), hypertension (OR 4.772, 95%CI 2.148-10.600, p < 0.001), postoperative renal replacement therapy (OR: 2.06, 95%CI 1.312-3.246, p = 0.002), need for re-exploration for bleeding (OR 2.53, 95% CI 1.684-3.820, p < 0.01), pericardial effusion (OR 2.30, 95%CI 1.205-4.390, p = 0.012), wound healing disorder (OR 2.301, 95%CI 1.038-5.099, p = 0.040), discharge ECG rhythm (OR 2.995, 95%CI 1.819-4.929, p < 0.001) and a biological CVG (OR 2.481, 95%CI 1.675-3.674, p < 0.001) were identified as independent predictors of increased mortality (Table 11).

Table 10. Independent predictors of late overall mortality in multivariate Cox regression analysis.

Variables	Patients (n=273)		
	OR	95% CI	p-value
Age	1.046	1.023-1.069	<0.001
Pulmonary hypertension	1.810	1.159-2.825	0.009
Pre-operative ECG rhythm	1.726	1.066-2.795	0.026
Hypertension	4.772	2.148-10.600	<0.001
Re-exploration for bleeding	4.502	2.404-8.431	<0.001
Postoperative renal replacement therapy	2.064	1.312-3.246	0.002
Pericardial effusion	2.300	1.205-4.390	0.012
Wound healing disorder	2.301	1.038-5.099	0.040
Discharge rhythm	2.995	1.819-4.929	<0.001
Biological valve graft	2.481	1.675-3.674	<0.001

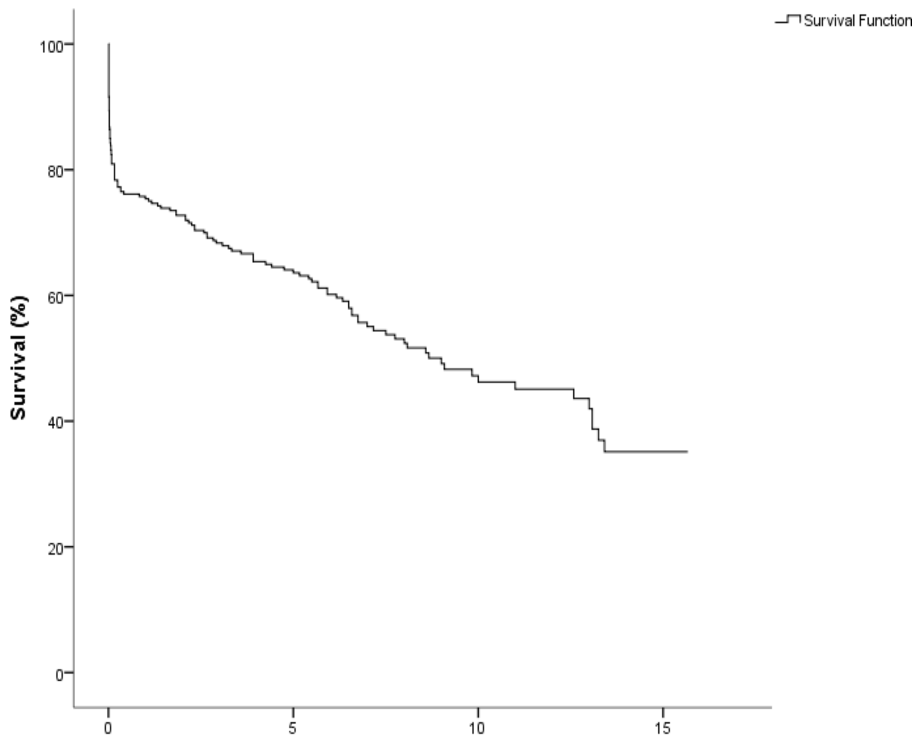

Figure 8. Kaplan-Meier curve of survival probability for all 273 patients who underwent the Bentall-de Bono procedure.

Kaplan-Meier estimated overall survival rates for the 273 patients (including hospital deaths) were 75.4 ± 2.6 %, 63.6 ± 3.0 %, 46.2 ± 3.7 % and 35.1 ± 4.7% at 1, 5, 10 and 15 years, respectively (Figure 8). The mean survival in our study was 8.6 ± 0.4 years (CI: 7.7-9.4 years).

There was a significant difference in the survival between the groups in favour of the dissection group (p = 0.008; Figure 9). After the early deaths (<30 days) of nearly a fifth of the dissection patients, survival rates remained somewhat stable throughout the follow-up period with estimates of 70.1 ± 6.8% and 63.4 ± 7.6% at 5 and 10 years respectively. The dissection group also surpassed the overall mean survival rate for the whole population amounting to 9.8 ± 0.9 years. Although only less than 10% of patients with other pathologies were subject to early mortality the survival rate of the group decreased gradually over time (71.3 ± 4.1% and 47.3 ± 5.4% at 5 and 10 years, respectively). The chart also suggests that endocarditis patients maintained the lowest survival rate throughout the whole follow-up period with 51.2 ± 5.2 % and 37.1 ± 6.6 % and at 5 and 10 years respectively.

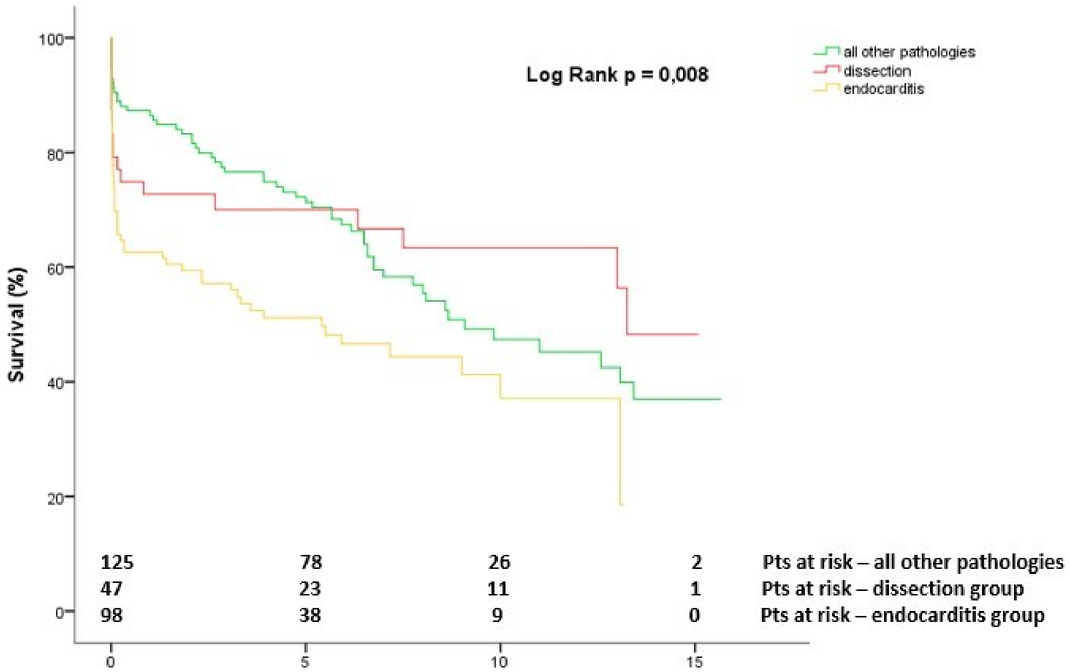

Figure 9. Kaplan-Meier estimates showing the influence of Aortic/AV pathology on the survival probability.

Overall survival rates of patients divided by the time of intervention also showed a significant difference in favour of the patients who underwent emergency surgery (p = 0.007; Figure 10). The lowest survival showed the group of urgent indication to surgery with rates of 46.3 ± 6.3 %, 31.8 ± 6.7 % and 25.5 ± 7.8% at 5, 10 and 15 years. Surprisingly, after the preliminary deaths of almost a quarter of the emergency patients, their rates remained fairly constant (60.6 ± 6.3% at year 5 and 54.1 ± 7.2% at year 10). Although only 5% of the elective group patients perished in under 30 days after surgery their overall survival declined progressively and thus reaching a lower rate than the emergency group (72.3 ± 3.8% and 49.1 ± 5.4% at 5 and 10 years).

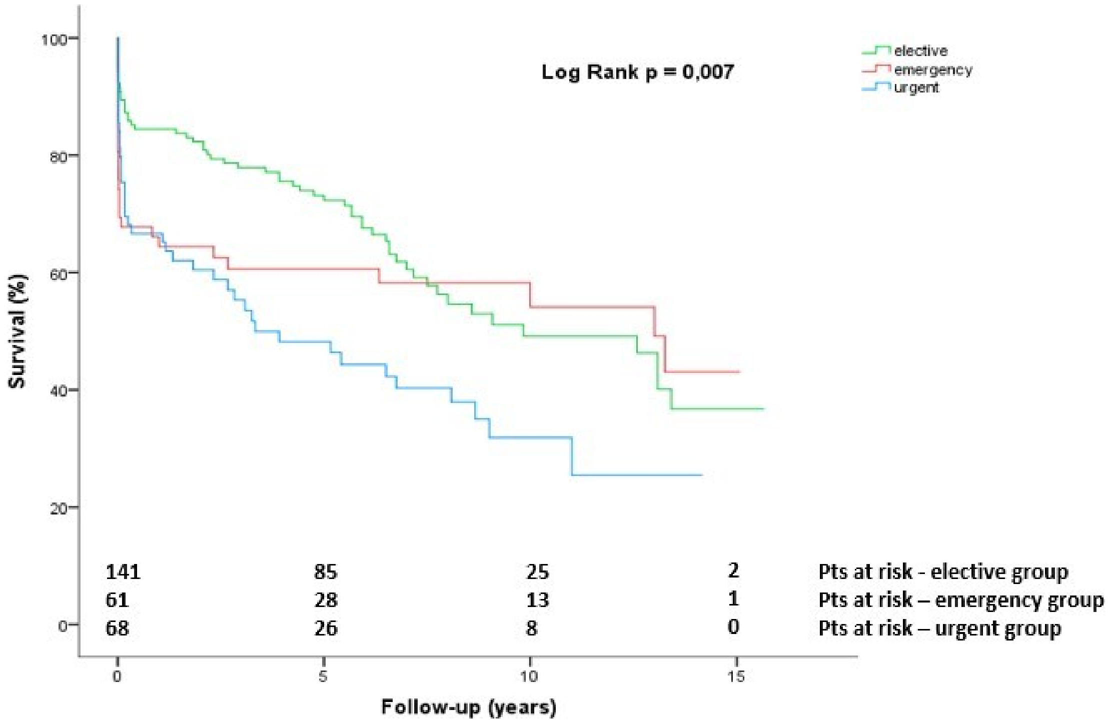

Figure 10. Kaplan-Meier estimates showing the influence of time of operation on the survival probability.

As shown in Figure 11 there is a significant discrepancy between survival rates of patients who received biological CVG and those who underwent mechanical CVG ($p<0.001$). After 5 years only half of the patients from the biological prosthesis group survived (55.2 ± 4.0%), with the survival rate further decreasing to 30.8 ± 5.4% at year 10 of observation. In contrast, more than three quarters (76.1 ± 4.2 %) of the mechanical group population were alive after 5 years, before slightly dropping to 63.9 ± 5.2% at 10 years of follow-up.

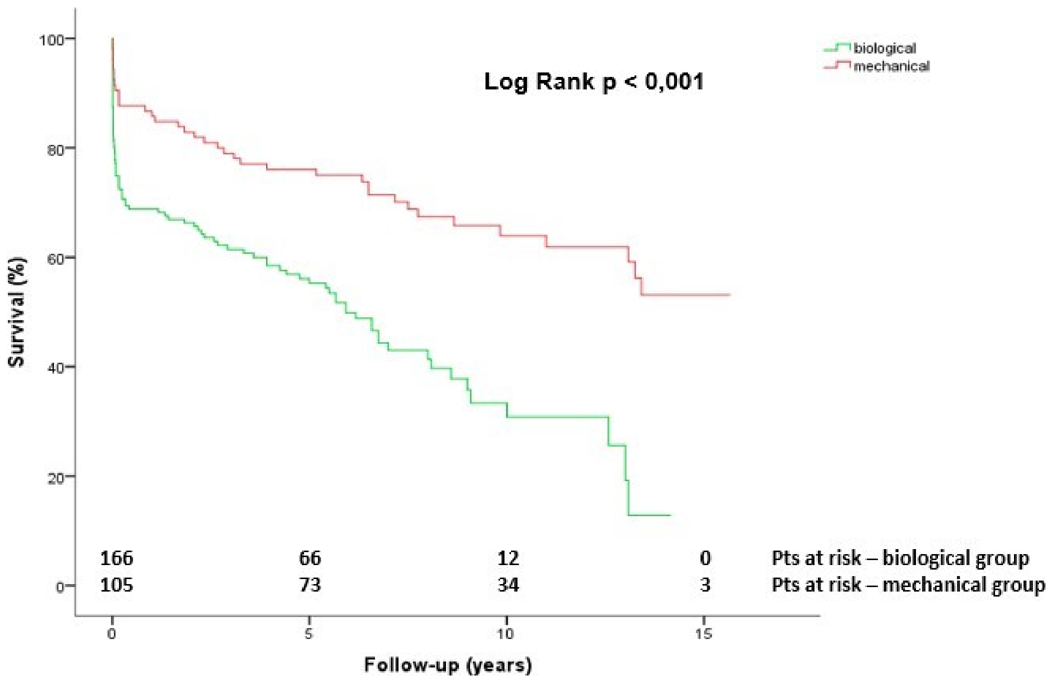

Figure 11. Kaplan-Meier estimates showing the influence of valve prosthesis on the survival probability.

3.3.2 Reoperation

Only 11 (8.2%) of the surviving patients required reoperation during the follow-up period. The main cause for reoperation was endocarditis, followed by valve dysfunction and pseudoaneurysm of the CVG. In the overall population, the 5- and 10-year freedom from reoperation of the AV and/or aortic root was 97.2 ± 1.0% and 95.2 ± 1.5% respectively (Figure 12). There was no statistically significant difference in the freedom from reoperation of the AV and/or aortic root between the groups according to the pathology ($p = 0.545$). The freedom from reoperation rate at 10 years was 95.5 ± 4.4% in the dissection group, 96.9 ± 2.2% in the endocarditis group and 94.1 ± 2.2% in all other pathologies group (Figure 13). No significant difference in the freedom of reoperation rates were found between the elective, emergency and urgent groups (0.504; Figure 14), as well as between the biological and mechanical CVG group ($p = 0.853$; Figure 15).

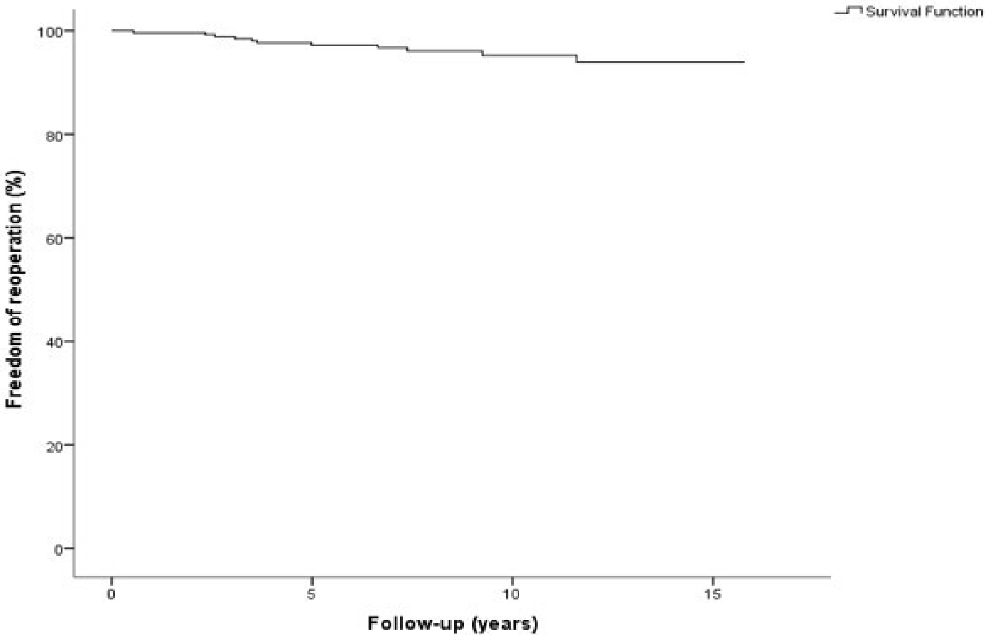

Figure 12. Kaplan-Meier estimated freedom of from AV and/or aortic root reoperation.

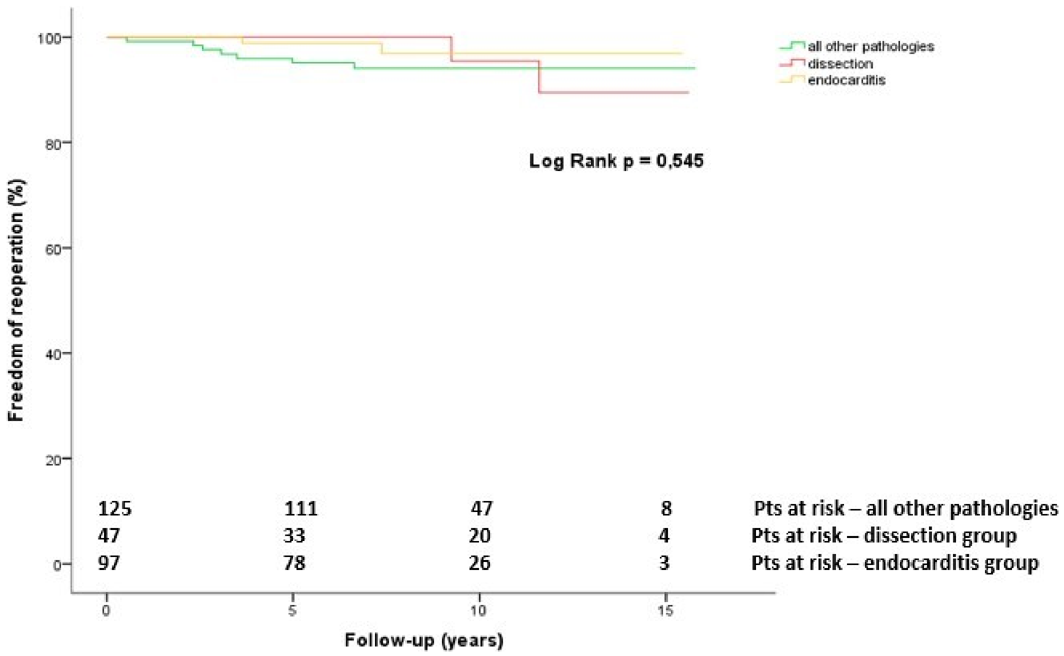

Figure 13. Kaplan-Meier estimated freedom from AV and/or aortic root reoperation according to the subgroups.

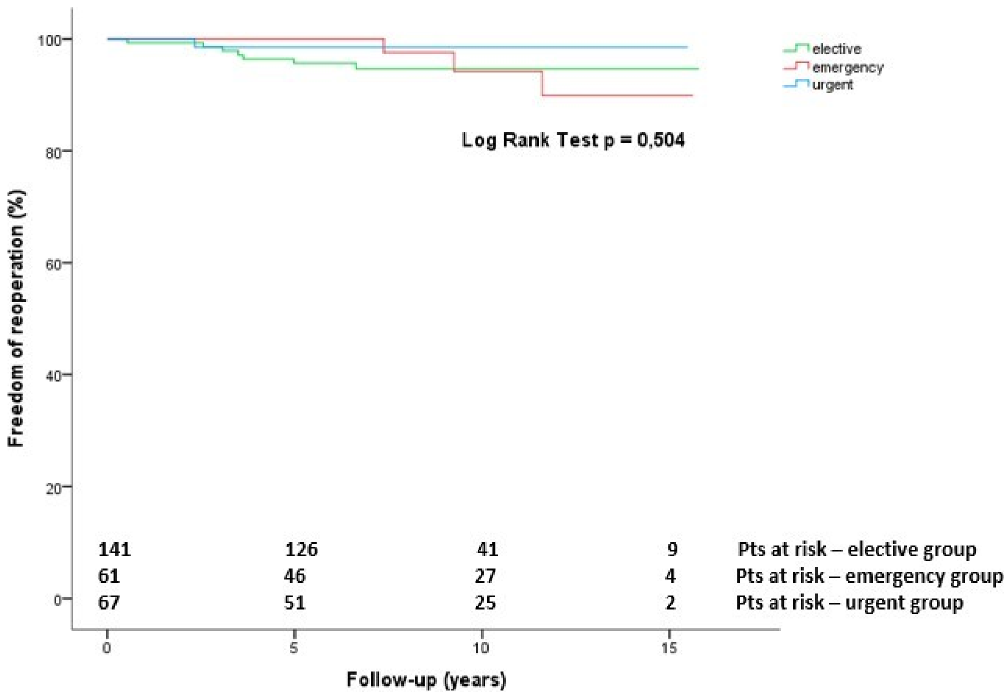

Figure 14. Kaplan-Meier estimated freedom of reoperation according to time of operation.

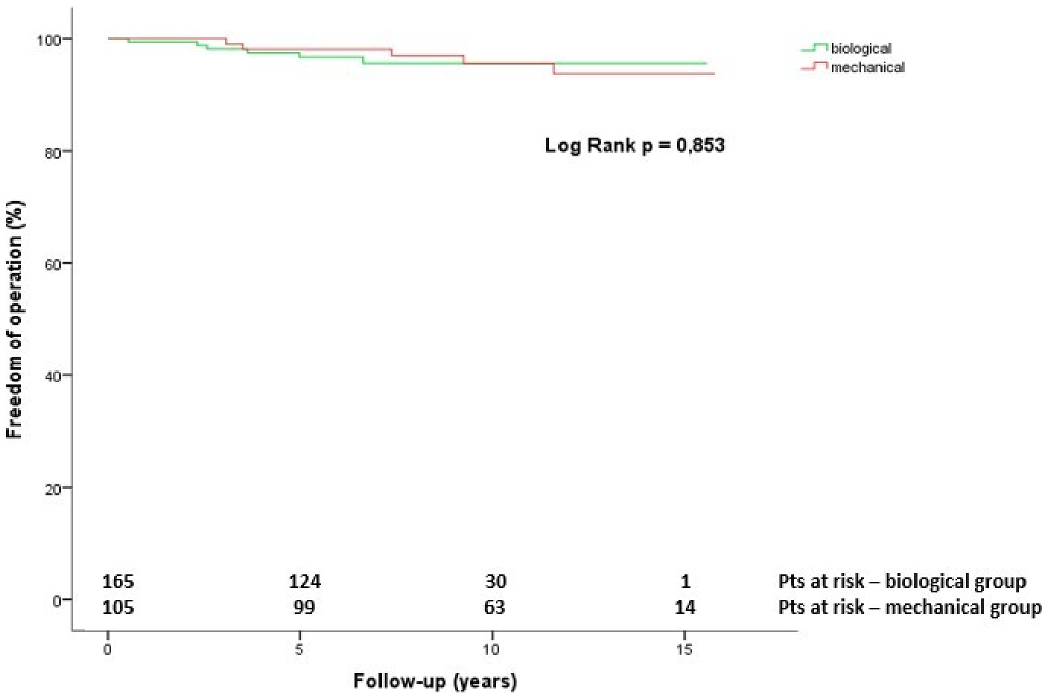

Figure 15. Kaplan-Meier estimated freedom of reoperation according to AV graft type.

3.3.3 Adverse follow-up events

In the follow-up period, 8 patients (6%) suffered from thrombo-embolic event. The overall 10-year freedom from thrombo-embolic events was 97.6 ± 1.0% (Figure

16). The freedom rate from thromboembolic events between the different groups showed no significant difference (p = 0.107, p = 0.709, p = 0.248 for Figures 17-19). We defined AV prosthesis dysfunction as a structural deterioration of the

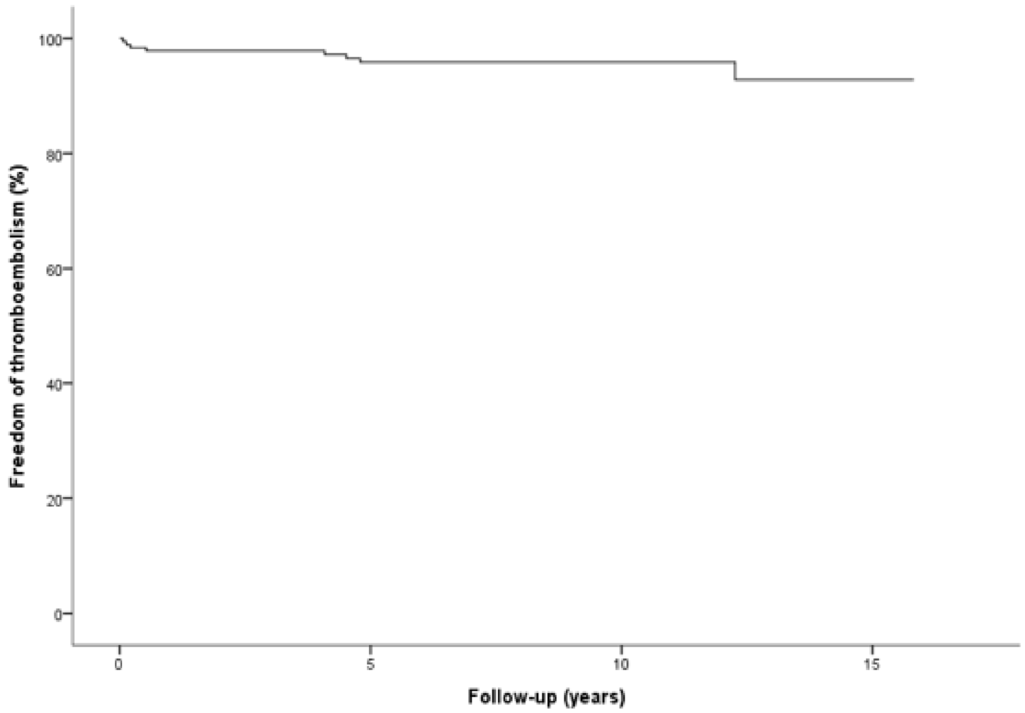

Figure 16. Kaplan-Meier estimated overall freedom of thromboembolic events for the total study.

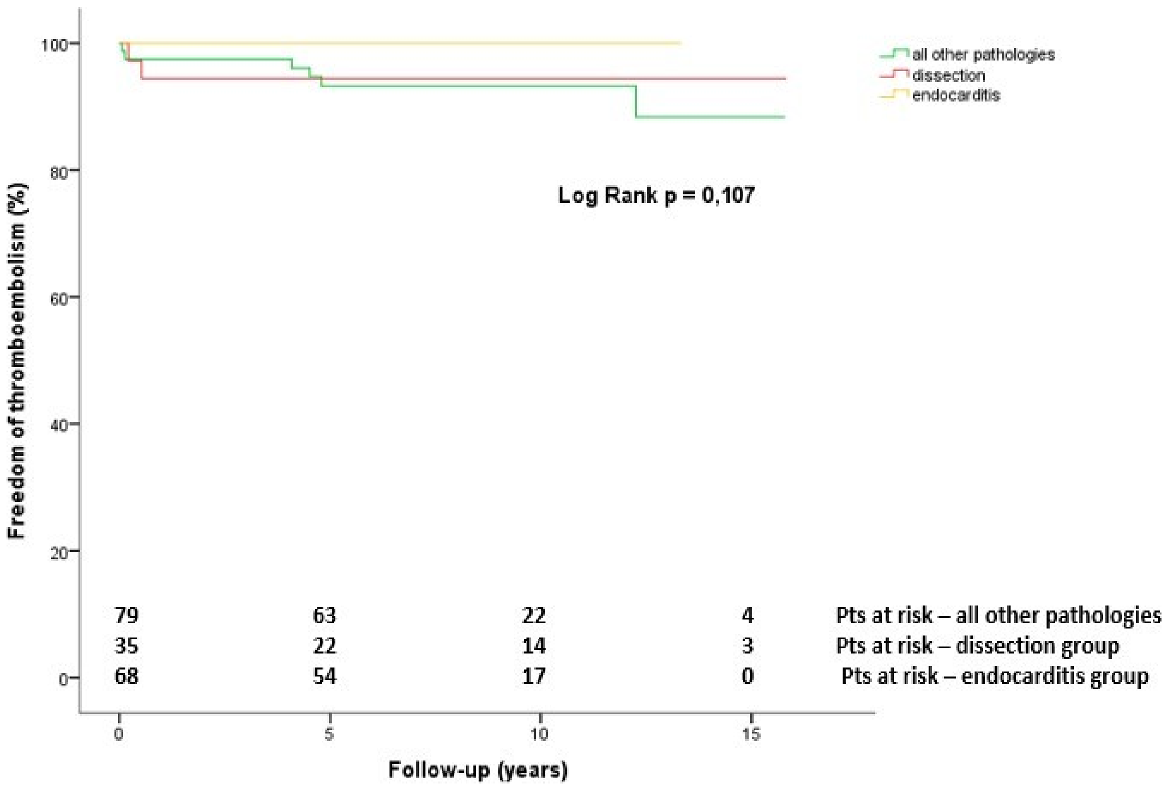

Figure 17. Kaplan-Meier estimated freedom of thromboembolic events according to AV pathology.

valve graft or any form of postoperative valve stenosis or insufficiency. The freedom rate from AV prosthesis dysfunction also showed no significant difference between the groups (p = 0.127, p = 0.207, p = 0.333; Figures 21-23). The estimated 10-year freedom rate from AV graft dysfunction in the total population was 96.4 ± 1.8% (Figure 20). Kaplan-Meier estimated freedom of thromboembolic events according to time of operation.

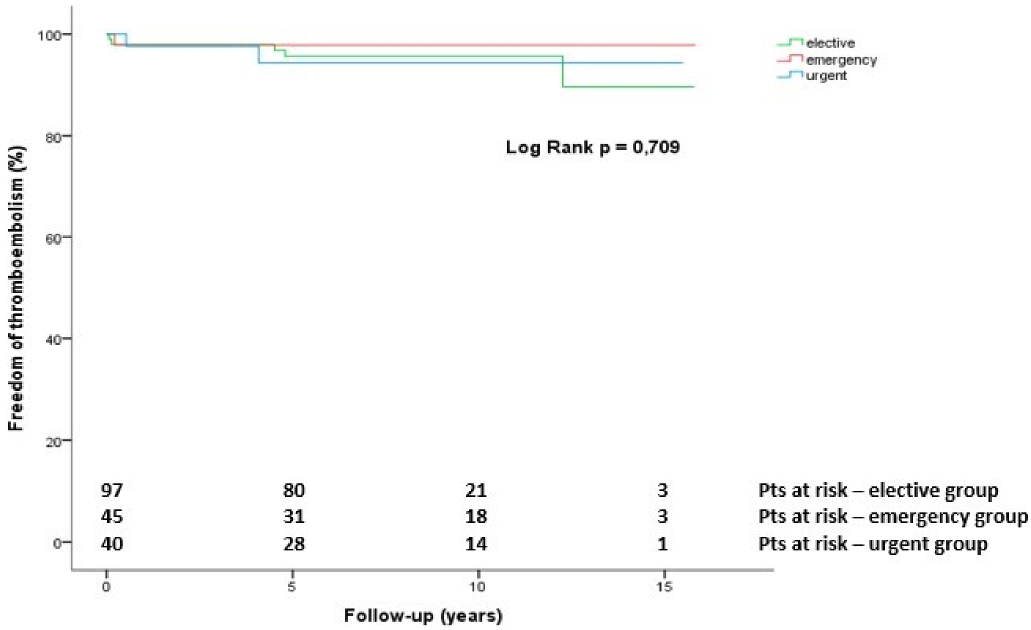

Figure 18. Kaplan-Meier estimated freedom of thromboembolic events according to time of operation

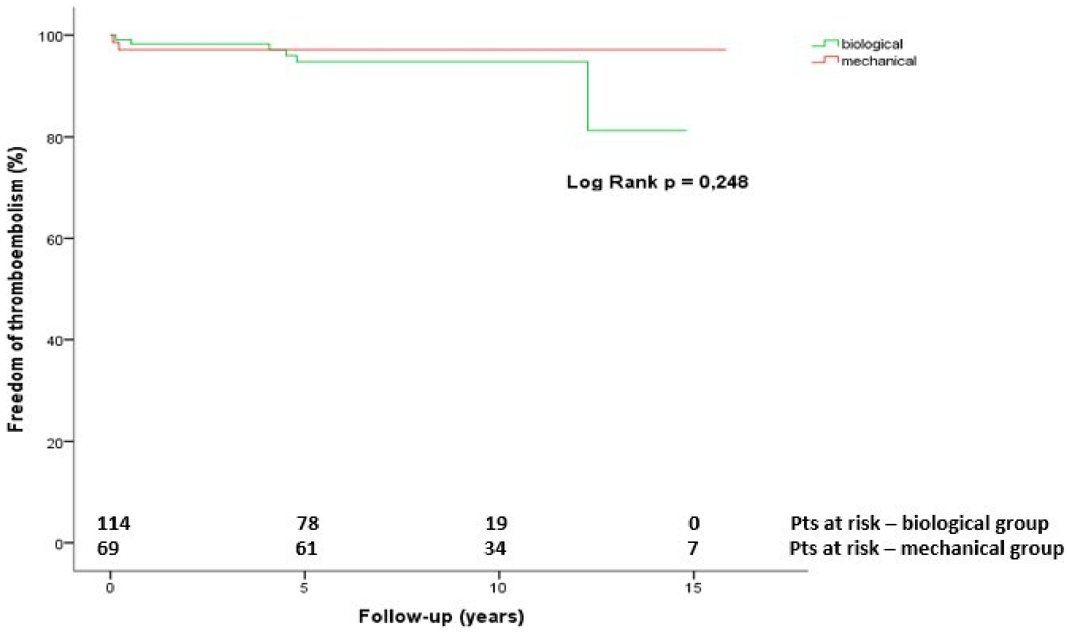

Figure 19. Kaplan-Meier estimated freedom of thromboembolic events according to AV graft type.

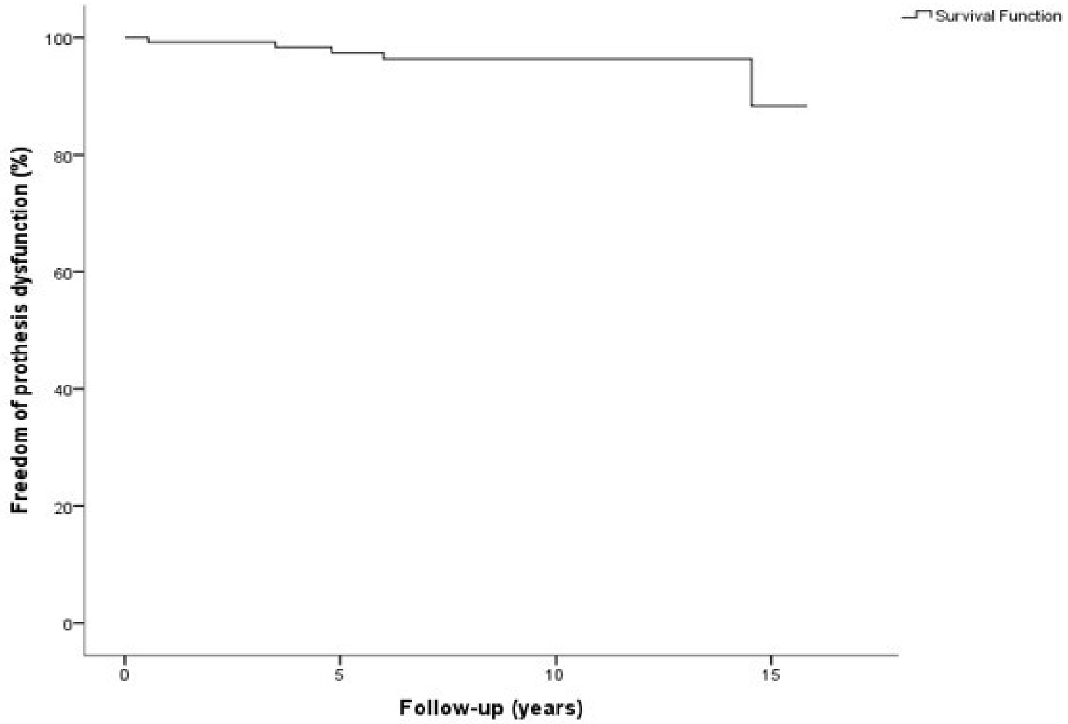

Figure 20. Kaplan-Meier estimated overall freedom of AV prosthesis dysfunction for the total study population.

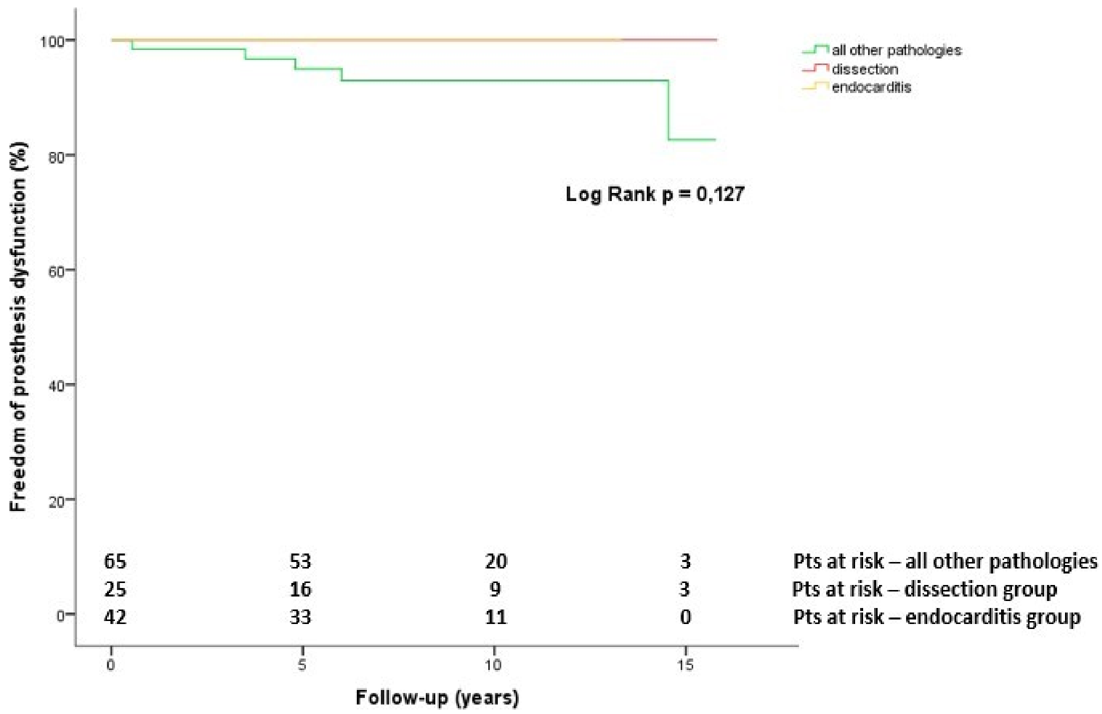

Figure 21. Kaplan-Meier estimated freedom of AV prosthesis dysfunction according to AV pathology.

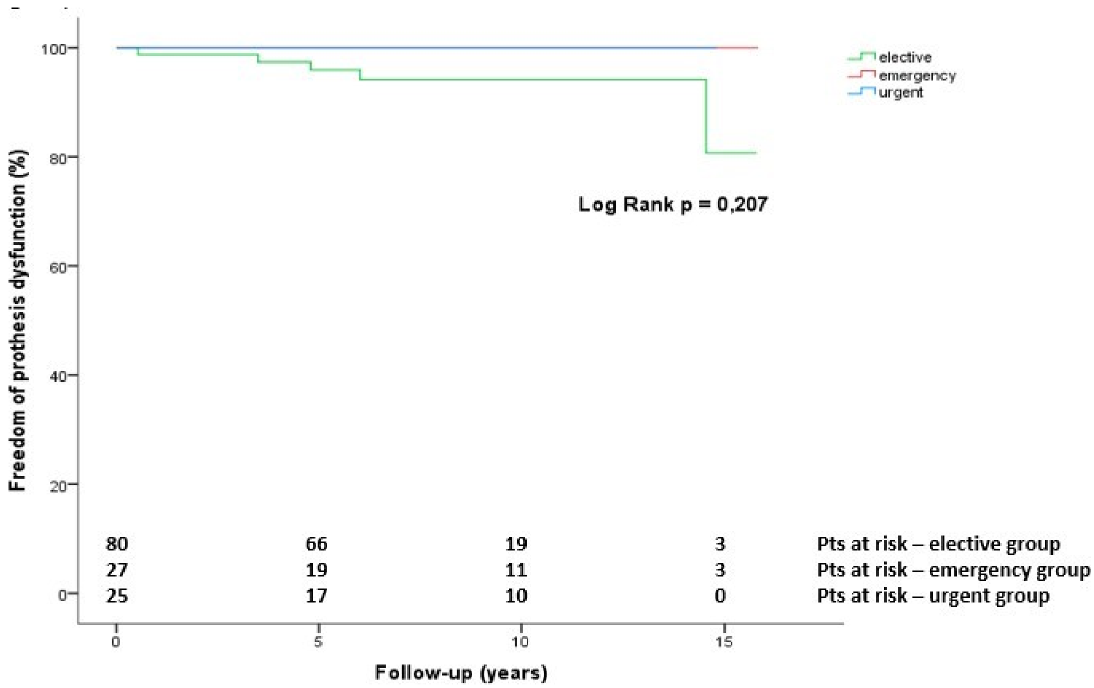

Figure 22. Kaplan-Meier estimated freedom of AV prosthesis dysfunction according to time of operation.

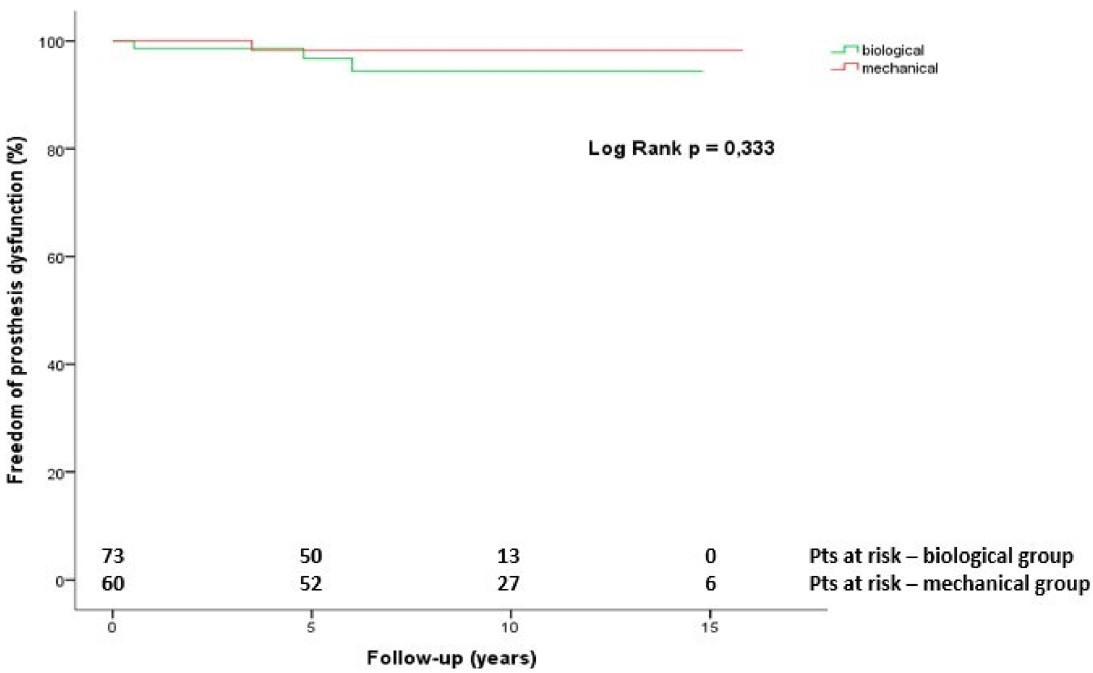

Figure 23. Kaplan-Meier estimated freedom of AV prosthesis dysfunction according to AV graft type.

The overall freedom from endocarditis was 97.8 ± 1.0 % at 10 years (Figure 24). A statistically significant difference between the different groups could not be detected ($p = 0.689$, $p = 0.592$, $p = 0.217$; Figures 25-27).

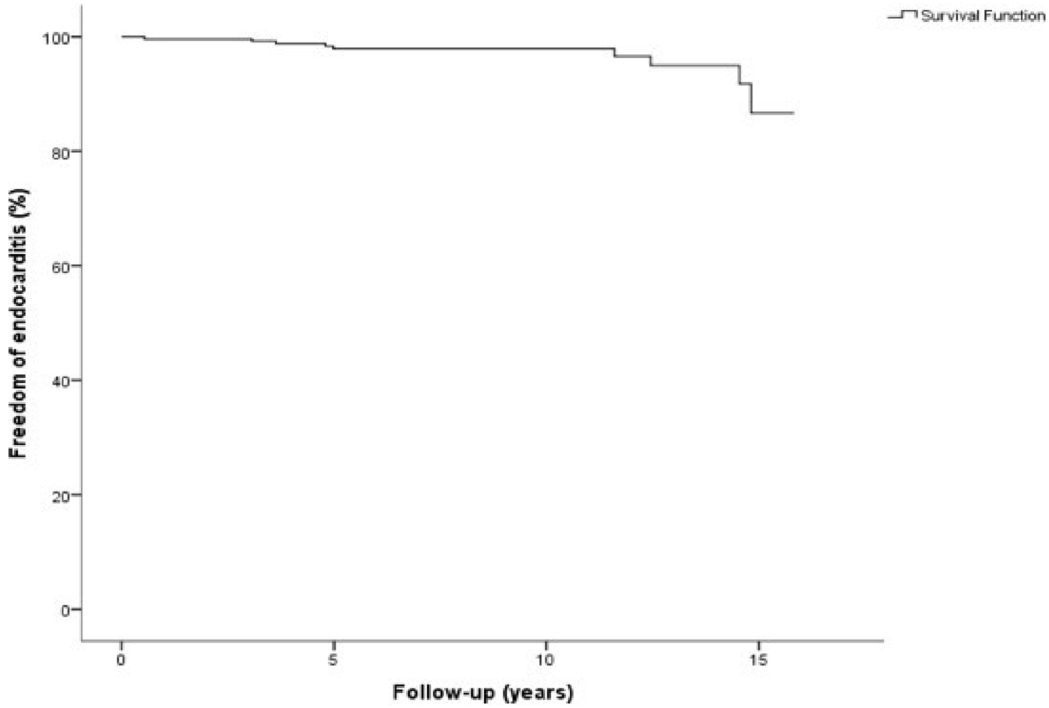

Figure 24. Kaplan-Meier estimated overall freedom of endocarditis for the total study population.

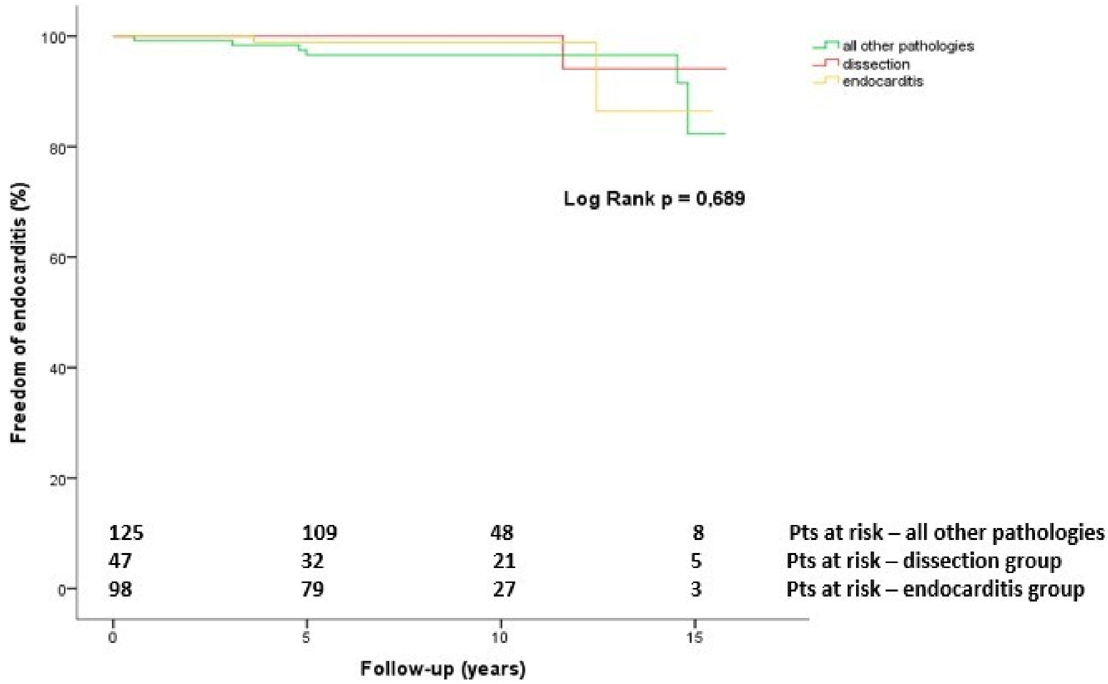

Figure 25. Kaplan-Meier estimated freedom of endocarditis according to AV pathology.

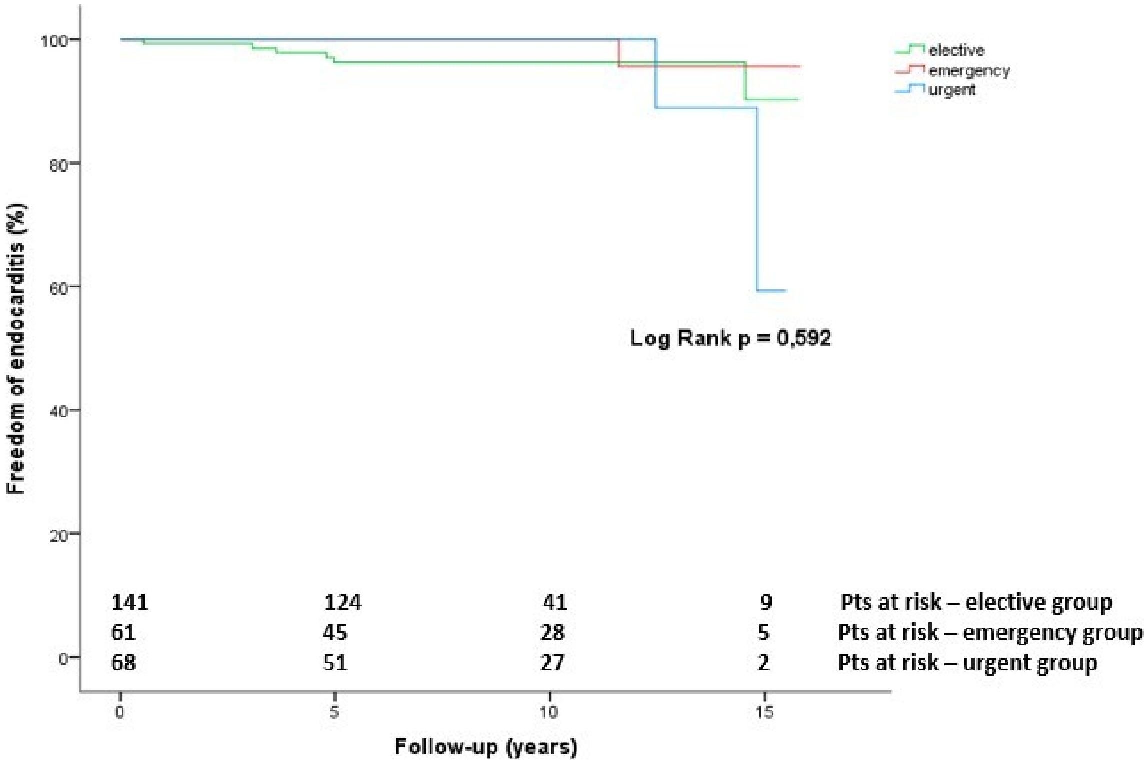

Figure 26. Kaplan-Meier estimated freedom of endocarditis according to time of operation.

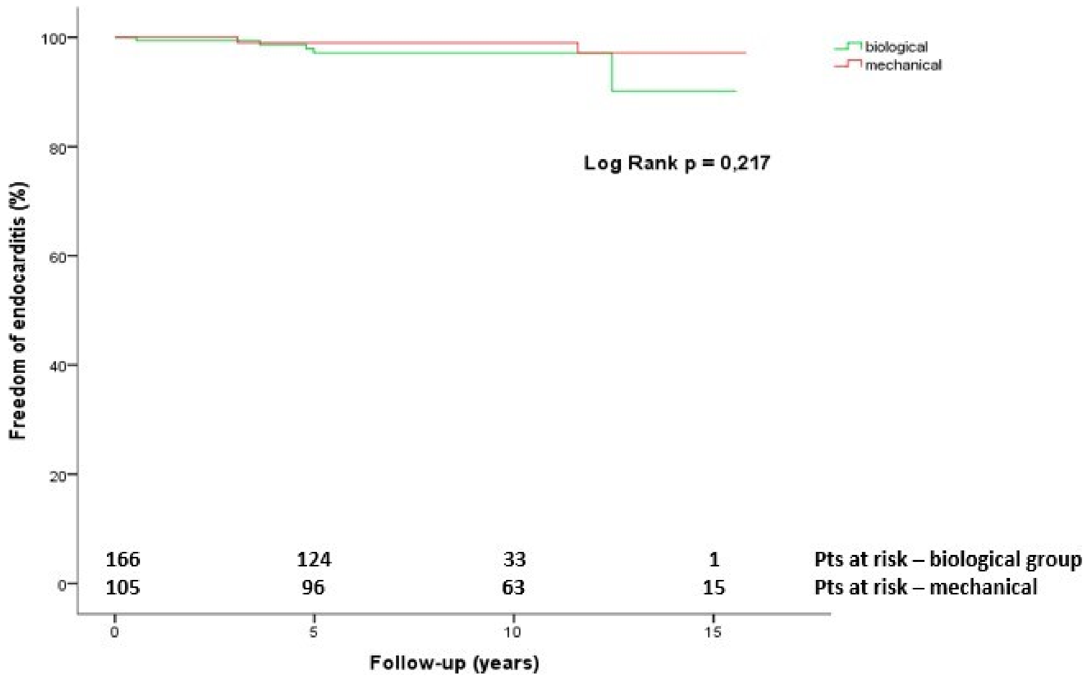

Figure 27. Kaplan-Meier estimated freedom of endocarditis according to AV graft type.

3.3.4 Follow-up echocardiography

In the follow-up echocardiography a significant decrease in the IVSd thickness was revealed compared to the postoperative (discharge) echocardiography (13.3 ± 2.4 mm to 12.2 ± 1.9 mm; p<0.001). The EF also improved over the course of follow-up (54.2 ± 11.5 % to 57.8 ± 9.1 %; p<0.001). The AV peak and mean gradients also showed improvement with values going from 23.1 ± 0.9mmHg to 18.7 ± 0.9 mmHg and from 13.7 ± 0.6mmHg to 9.9 ± 0.5 mmHg respectively. Over the time, a slight decrease in AV graft function could be monitored. Grade I AR was present in 42 patients (31.4%) and grade II AR in 2 patients (1.5%). MR and TR were still present in 83 (65.6%) and 65 (48.9%) patients respectively. No significant AV stenosis was detected in any of the patients in the study population.

Table 11. Follow-up echocardiography data.

Variable	Overall (n=133)	Dissection Group (n=26)	Endocarditis Group (n=42)	All other pathologies (n=65)	p-value
LVEDd (mm)	52.21	54.88	52.91	50.08	0.42
IVSd (mm)	12.24	12.05	11.86	12.55	0.27
EF (%)	57.80	57.52	57.44	58.14	0.26
AV-Gradient max (mmHg)	18.73	17.83	18.12	19.67	0.03
AV-Gradient mean (mmHg)	9.94	9.73	9.51	10.34	0.683
Ascending aortic diameter	31.26	31.39	32.54	30.79	0.67
AR					0.11
Grade I	42 (31.6%)	10 (38%)	6 (14%)	26 (40%)	
Grade II	2 (1.5%)	0	2 (5%)	0	
Grade III	0	0	0	0	
Grade IV	0	0	0	0	
MV regurgitation					0.71
Grade I	59 (44.4%)	11 (42%)	18 (43%)	30 (46%)	
Grade II	23 (17.3%)	3 (12%)	8 (19%)	12 (18%)	
Grade III	1 (0.7%)	0	1 (2%)	0	
Grade IV	0	0	0	0	
TV regurgitation					0.82
Grade I	55 (41.4%)	8 (31%)	19 (45%)	24 (4%)	
Grade II	7 (5.3%)	1 (4%)	1 (2%)	5 (8%)	
Grade III	3 (2.2%)	1 (4%)	1 (2%)	1 (2%)	
Grade IV	0	0	0	0	

AR, aortic regurgitation; AV, aortic valve; EF, ejection fraction; IVSd, diastolic interventricular septal wall thickness, LVEDd, left ventricular end-diastolic diameter; MV, mitral valve; TV, tricuspid valve

4. Discussion

Since its introduction in 1968 by Bentall and de Bono[6], AVRR using a CVG has been considered to be the gold standard for the treatment for a variety of AV, root and ascending aorta diseases, including lesions associated with type A dissection, endocarditis and annulo-aortic ectasia with an irreparable AV among others.[33] In this procedure, the affected part of the ascending aorta and the AV are replaced by a CVG carrying either a mechanical or biological AV prosthesis. Over the last few decades several modifications of the original procedure have been established and have improved clinical outcomes.[34] With standardization of the technique and thorough planning satisfactory results can be achieved.[35] Due to its proven effectiveness and satisfactory results obtained by experienced surgeons it can be successfully applied to a wide spectrum of aortic diseases.[25,36]

However, the BD procedure exposes patients to the drawbacks associated with artificial valves, such as structural valve deterioration for biological grafts, the need for life-long anticoagulation for mechanical grafts, and the amplified risk of endocarditis and thrombo-embolism for both.[33] An alternative to the BD procedure, avoiding the disadvantages of prosthetic heart valves, has been introduced by David et al.[9,37] Patients suffering from isolated aortic pathologies, such as aortic root or ascending aorta aneurysms often have normal or minimally damaged aortic cusps that can be preserved. This operation offers a reliable option for patients where anticoagulation is contraindicated with satisfactory long-term results.[38,39] However, the current study does not include patients undergoing valve-sparing surgery and it reports only on our experience with CVG replacement. Its goal was to determine whether there are any differences in the early and late outcomes between patients with different conditions and compare the results biological and mechanical CVG.

A total of 273 patients were examined. In our experience the mean survival was 8.6 ± 0.4 years (CI: 7.7-9.4 years) after procedure and the overall survival rate at 10 years 46.2 ± 3.7%. Several other studies have shown higher survival rates, however their patients were younger and showed lower risk profile.[33,34,40,41] As a well-established centre for complex aortic pathologies and AV and root repair techniques our department generally admit severely diseased patients. Early mortality (<30 days) in our cohort was 17.2%, which is higher than that estimated by Mookhoek et al. in their meta-analysis (5.6%).[3] However, given the complexity of our cases, the high number of reoperations and the patients' risk profiles we evaluate our overall survival as satisfactory and in line with those reported by others.[36,42]

The most interesting feature of our study concerns the statistically significant higher survival rate in patients with aortic dissection as the main surgical indication compared to those with endocarditis or other aortic diseases ($p<0.001$). This contradicts other studies which have found long-term survival to be statistically less favourable for patients with type A dissection[43]. Patients with dissection simultaneously had the lowest total mortality rate among the population – 37.5%. This could be explained by the fact that patients with type A dissection were younger, had therefore fewer comorbidities compared to other patients (Table 2) and were subject to fewer concomitant surgeries during their hospital stays. In our series, the mean age of the dissection group was 54.8 ± 14.5 years, whereas the mean age of the other two groups were 65.8 ± 12.8 and 66.2 ± 10.4 for endocarditis and other aortic pathologies, respectively. Another reason for the better survival rate of dissection patients was that they experienced less in-hospital and follow-up complications.

Patients with endocarditis had the worst survival rate of all groups. This could be explained by the high number of comorbidities. Endocarditis patients had the most previous cardiac surgeries in their history with 79 of the 99 (79.8%) patients prior to the BD procedure. The endocarditis group had the highest number of patients who were diagnosed with heart failure upon the admission. Due to the infective endocarditis' association with septic-embolic phenomena many of these patients suffered from neurological disorders and renal insufficiency. Endocarditis patients also had the highest 30-day mortality and late mortality rates from the whole population, with 26.3% and 54.5%, respectively. Together with thromboembolism, endocarditis was the most common late postoperative complication. Similar to the study of Pantaleo et al.[35] we confirmed infective endocarditis as the most serious cause of aortic reintervention with 8 of the 11 patients undergoing reoperation developing endocarditis during the observation period. It is a standard policy to replace the infected CVG and fitting antibiotic prophylaxis should be considered as the main pre-emptive measure.[36]

Observing the population according to the time of operation we discovered that for urgent surgery, the patients had a significantly lower long-term survival rate that those undergoing elective or emergency procedures (p = 0.007). Because endocarditis patients were usually operated on an urgent or elective basis and since they have the lowest survival probability it is comprehensible why the urgent group has a lower survival rate than the others. Other studies argue that elective and carefully planned surgery significantly reduce mortality and offers a higher long-term survival rate.[33,44] Simultaneously, patients operated on an emergency basis had the highest survival rate of all groups. Again, we presume that this occurred due to the younger age of patients who suffered from type A dissection. For 44 of all 48 dissection patients the time of intervention was labelled as an emergency. Other studies, however, argue that emergency operation has a negative impact on in-hospital and long-term survival.[2,40]

In our series, we found a significantly lower survival probability for patients who received a biological CVG, compared to the patients receiving a mechanical CVG (p<0.001). There are several probable explanations for this: 1. higher mean age (70 vs 55 years), 2. increased number of patients admitted with a heart failure (72 vs 26 patients), 3.greater number of previous heart surgeries (85 vs 28 previous operations), 4.increased burden of atherosclerosis and CAD (78 vs 22 patients), 5. more patients with COPD (69 vs 21 patients) and 6. more patients undergoing a redo BD operation (82 vs 27 patients). The discrepancy in mortality is predictable, given the practice of implanting biological CVG in elderly patients and those with multiple life-limiting comorbidities.[2] Furthermore, we identified biological CVG as independent predictor of overall mortality (p<0.001). Our results were in line with those of other studies, which also recommend the use of mechanical CVG as the first-choice treatment for aortic root pathology if no contraindications are present.[35,45] Despite the life-long intake of anticoagulants required for mechanical CVG, there was no occurrence of major haemorrhagic or thromboembolic events at the follow-up.

Regarding patients with Marfan syndrome our study showed a survival probability of 100% at 15 years, which was significantly higher than that of the whole population (p = 0.024), as 5 of the 7 patients were still alive after the observation period and 2 patients were lost to follow-up. Four patients suffered from ATAAD, 1 from endocarditis and 2 from other AV pathologies, such as annulo-aortic ectasia or AR. There were no significant differences between Marfan patients with aortic dissection and those without. Five patients were operated on an emergency basis, 1 was labelled as urgent and 1 underwent an elective procedure. All 7 patients received mechanical CVG. No patient needed a reoperation during the observation period. This highlights the practicality of the Bentall operation as a treatment of choice for patients with Marfan syndrome, which can be carried out with low operative mortality and acceptable long-term survival.[33] In our study, the rate of freedom from reoperation, endocarditis and thrombo-embolic events for those patients was higher than that of the other patients, which contrasts the study of Pacini et al.[36] It is widely debated whether Marfan syndrome is associated with a decreased long-term survival or not. Puluca et al. considered Marfan syndrome as an independent risk factor for long-term mortality[46], whereas Hagl et al. reported on the lack of statistically significant association between the disease and lower long-term survival.[25]

Regarding postoperative ventricular function our series showed that LV systolic function (EF) and NYHA functional class improved significantly at the follow-up, based on transthoracic echocardiography. Even though LVEDd did not decrease, IVSd thickness reduced and AV peak and mean gradients diminished during the long-term follow-up. The study of Deşer et al. showed similar results.[41]

In our study we concluded that the main cause of late reoperations was prosthetic valve endocarditis (8 of 11 patients). Only one patient developed a pseudoaneurysm formation of the proximal suture line and he underwent a successful reoperation. Freedom rate of reoperation was excellent and surpassed rates of other studies.[2,33,34,40,40] Complication rates were low with only 12% of surviving patients developing either endocarditis, thromboembolism or AV dysfunction. Similar to other studies, endocarditis was found to be the most common late complication.[47] Freedom from thrombo-embolism, bleeding, endocarditis and valve-related complications were satisfactory and also in line with other published studies.[33,36]

Numerous studies have shown different independent risk factors for death after the BD procedure.[2,34] We identified advanced age, poor preoperative NYHA functional class, previous cardiac surgery, diabetes, CAD, renal insufficiency, peripheral artery disease, biological CVG, concomitant surgery, postoperative re-exploration for bleeding, postoperative neurologic dysfunction and postoperative dialysis as predictors of early and late death.

Through our uni- and multivariate analysis we found that dissection, Marfan syndrome and emergency status did not prove to be independent risk factors for early or late mortality, similar to other studies.[25,34]

4.1 Study limitations

The lack of randomization and the retrospective nature of the study were the most significant limitations. Due to the retrospective design, the recording of events over such a long period of time is suboptimal and underreported, especially because some of the follow-up reports was done with telephone interviews and the response rate to the questionnaires was not 100% complete. The distribution of case numbers among the groups was relatively heterogeneous with different lengths of the follow-up. The echocardiographic follow-up examinations were not performed in all cases in our clinic and were partly incomplete. Surgeries were performed by a relatively large group of surgeons, and in many cases the decision to use a particular procedure depended on the individual surgeon's experience. Moreover, data collection during the earlier years of the study was incomplete and deficient, leading to some variables being excluded from the statistical analysis. Therefore, the significance and impact of these variables on early and late mortality could not be studied.

5. Conclusion

In conclusion, the AVRR with CVG and reimplantation of the coronary arteries (according to Bentall and De Bono) can be performed with low morbidity and acceptable mortality, as well as with appropriate functional early- and long-term results and a very low rate of reoperations or complications. Our single-centre study shows that even in high-risk populations of patients with complex aortic pathologies, AVRR should be the method of first choice when technically feasible. Mechanical valve prosthesis implantation could offer a long-time treatment option with a low occurrence of thrombo-embolic complications and no valve deterioration. Endocarditis and thrombo-embolism remain the most common late complications. The BD operation is a safe and durable treatment option for Marfan patients. Valve-related complications are rare, and AV functional status improves postoperatively. We can conclude that assessing the prosthetic valve function, EF, diameter of the aorta and the reimplanted coronary arteries, as well as morphological changes of the ascending aorta and the heart through echocardiography is extremely important for evaluating a successful postoperative outcome. The overall good short- and long-term results demonstrate that in specialized centres the BD operation, even when combined with other heart procedures, is linked to low postoperative adverse event rates, reasonable mortality and an acceptable quality of life.

6. Summary

Aortic valve (AV) and root replacement with composite graft and re-implantation of coronary arteries described first by Bentall and de Bono in 1968, is considered as a standard operation for treatment of different pathologies of the AV and aortic root. In centres where aortic valve and root repair techniques and Ross operation are well established, generally severely diseased patients remain indicated for this procedure. The aim of this study was to evaluate the early and long-term outcomes after Bentall-De Bono (BD) procedures in high-risk population with complex pathologies and multiple comorbidities.

Between 2005 and 2018, a total of 273 consecutive patients (median age 66 years; 23 % female) underwent AV and root replacement with composite-graft in so called button technique. We divided our population in the following groups: 1. acute type A aortic dissection group (ATAAD) (n = 48), 2. endocarditis group (n = 99) and 3. all other pathologies group (n = 126). The surgery has been performed emergent/urgent in 131 patients (49 %) and in 109 cases (40%) as a reoperation. Concomitant surgery was required in 97 patients (58%) and 167 patients (61%) received a biological composite-graft.

Follow-up was completed in 96% (10 patients lost to follow-up) with a mean of 8.6 years (range 0.1-15.7 years), counting a total of 1450 patient-years. Thirty-day mortality was 17% (46 patients). The overall estimated survival in 5 and 10 years was 64% ± 3%) and 46% ±4 %). Group comparison showed a significant difference in favour of patient from the dissection group ($p = 0.008$). Implantation of a biological valve graft was associated with lower survival probability ($p < 0.001$). There was no significant difference in the freedom of reoperation rate between the groups. The same applies for freedom of postoperative endocarditis, thromboembolic events, and aortic prosthesis dysfunction. According to the univariate and multivariate logistic regression analysis primarily postoperative neurological dysfunction (OR 5.45), hypertension (OR 4.8) peripheral artery disease (OR 4.4), re-exploration for bleeding (OR 3.37) and postoperative renal replacement therapy (OR 3.09) were identified as leading predictors of mortality.

In conclusion, the BD operation can be performed with acceptable short- and long-term results in high-risk patients with complex aortic pathologies in a centre with well-established AV repair and Ross operation program.

7. Zusammenfassung

Der Aortenklappen- und Aortenwurzelersatz mit einer klappentragenden Gefäßprothese und mit Reimplantation von Koronararterien, der erstmals 1968 von Bentall und De Bono beschrieben wurde, gilt als Standardoperation zur Behandlung verschiedener Pathologien der Aortenklappe und der Aortenwurzel. In Zentren, wo die Technik der Aortenklappen- und Aortenwurzelrekonstruktion und die Ross-Operation gut etabliert sind, bleiben in der Regel nur schwer erkrankte Patienten für dieses Verfahren indiziert. Ziel dieser Studie war es, die Früh- und Langzeitergebnisse nach Bentall-De Bono (BD) Operation bei Hochrisikopopulationen mit komplexen Pathologien und mit multiplen Komorbiditäten auszuwerten.

Zwischen 2005 und 2018 wurden insgesamt 273 Patienten (Altersmedian66 Jahre; 23 % weiblich) einem Aortenklappen- und Wurzelersatz mit klappentragender Gefäßprothese in der sogenannten Button-Technik unterzogen. Diese Kohorte wurde in die folgenden Gruppen unterteilt: 1. Gruppe mit akuter Typ A Aortendissektion (n = 48), 2. Gruppe mit Endokarditis (n = 99) und 3. Gruppe mit allen anderen Pathologien (n = 126). Die Operation wurde bei 131 Patienten (49%) als Notfall oder dringliche Operation und in 109 Fällen (40%) als Re-Operation durchgeführt. Eine begleitende Operation der Koronararterien, der Mitral- oder Trikuspidalklappe war bei 97 Patienten (58%) erforderlich und 167 Patienten (61%) erhielten eine biologische Klappenprothese.

Follow-up wurde bei 96% der Patienten abgeschlossen (10 Patienten gingen verloren), mit einem Mittelwert von 8,6 Jahren (Range 0,1-15,7 Jahre), wobei insgesamt 1450 Patienten-Jahre gezählt wurden. Die 30-Tage-Mortalität betrug 17% (46 Patienten). Das geschätzte Gesamtüberleben nach 5 und 10 Jahren betrug 64% ± 3%) und 46% ± 4%). Nach Vergleich der Gruppen zeigte sich ein signifikanter Unterschied zugunsten der Patienten aus der Dissektionsgruppe ($p = 0,008$). Das Einsetzen eines biologischen Klappentransplantats war mit einer geringeren Überlebenswahrscheinlichkeit verbunden ($p < 0,001$). Es gab keinen signifikanten Unterschied zwischen den Gruppen in Bezug auf die Freiheit von Reoperation. Das Gleiche gilt für die Freiheit von postoperativer Endokarditis, thromboembolischen Ereignissen und Fehlfunktion der Aortenprothese. Nach der

univariaten und multivariaten Regressionsanalyse wurden vor allem postoperative neurologische Funktionsstörungen (OR 5,45), Bluthochdruck (OR 4,8), periphere arterielle Verschlusskrankheit (OR 4,4), Re-Sternotomie bei Nachblutung (OR 3,37) und postoperative Nierenersatztherapie (OR 3,09) als wichtigste Prädiktoren für die Sterblichkeit identifiziert.

Zusammenfassend lässt sich sagen, dass die BD-Operation mit akzeptablen Kurz- und Langzeitergebnissen bei Hochrisikopatienten mit komplexen Aortenpathologien in einem Zentrum mit einem gut etablierten Programm für Aortenklappenrekonstruktionen und Ross-Operation durchgeführt werden kann.

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