UNIVERSITÉ DE NANTES

———

FACULTÉ DE MÉDECINE

———

Année : 2021 N°

THÈSE

pour le

DIPLOME D'ETAT DE DOCTEUR EN MEDECINE

DES de Cardiologie et Maladies Vasculaires

par

Robin LE RUZ

———

Présentée et soutenue publiquement le 16 mars 2021

———

Edwards SAPIEN XT Transcatheter Pulmonary Valve Implantation: Long-term outcomes in a French Registry

———

Président : Monsieur le Professeur Patrice GUERIN

Directeur de thèse : Monsieur le Docteur Julien PLESSIS

Remerciements

A mon directeur de thèse, Monsieur le Docteur Julien PLESSIS, qui m'encadre depuis mes débuts et sur qui j'ai toujours pu compter pour des conseils avisés et sages. Merci pour tes innombrables enseignements, ton humilité infaillible et ta bonne humeur imperturbable. L'amitié qui nous rassemble aura marqué mon internat, et je te suis reconnaissant pour ton investissement tout au long de ma formation.

Au président du jury, Monsieur le Professeur Patrice GUERIN, pour votre confiance, votre implication dans la transmission du savoir et pour toutes ces opportunités et perspectives qui me sont données. En espérant que ce travail soit le premier d'une longue collaboration et que nombreux seront les projets à venir.

A Madame le Docteur Laurianne LE GLOAN, membre du jury, pour ta gentillesse, ta rigueur et ton goût pour l'enseignement.

A Monsieur le Docteur Sébastien HASCOET, membre du jury, pour votre disponibilité ayant permis ces temps d'échanges précieux et enrichissants autour de ce projet.

A Monsieur le Professeur Alban BARUTEAU, membre du jury, pour tes bons conseils et ton expertise.

A Monsieur le Professeur Olivier BARON, membre du jury, pour votre intérêt pour cette thématique, consolidant l'incontournable partenariat entre la chirurgie cardiaque et la cardiologie interventionnelle.

TABLE OF CONTENTS

I. Introduction

A. Congenital heart diseases and right ventricular outflow tract dysfunction

Congenital heart diseases incidence is almost 10 per 1000 live births (1). Due to a constant improvement in medical and surgical management in western countries, 90% of the children reach adulthood. Consequently, this resulted in an increased prevalence of patients known for a congenital heart defect, rising up to 1 in 150 all-comers (2). It is recognized that this evolution will still increasing, by approximately 60% per decade. However, mortality among that population remains higher, mostly because of late morbimortality related to heart failure or arrhythmias (2).

This is particularly true for congenital malformations requiring right ventricular outflow tract intervention, such as conotruncal abnormalities and critical aortic stenosis, that represent respectively 20% and 5% of all congenital heart diseases (3). Surgical repair can be achieved applying to multiple devices such as valved or non-valved tube-grafts, homografts or bioprosthesis and patch enlargement (Figure 1).

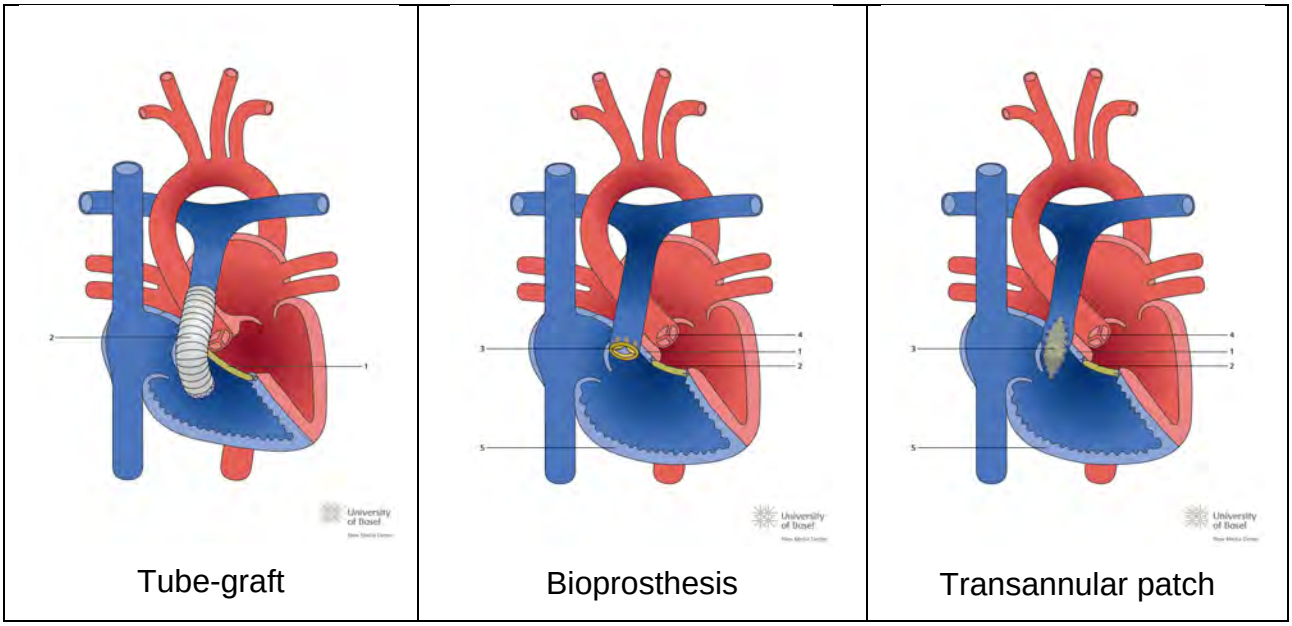


Figure 1. Illustration of the different modalities of right ventricular outflow tract surgical repair (*Illustrations taken from http://www.chd-diagrams.com)*

Two main issues arise from those techniques. Firstly, the transannular patch and non-valved conduits induce a severe pulmonary regurgitation because of the lack of efficient

leaflets to prevent backward flow of blood. Secondly valved tube-graft, bioprosthesis and homograft may deteriorate causing stenosis, insufficiency, or mixed lesion. Both aspects may induce right ventricular dysfunction overtime, then requiring surgical reintervention. The type of device that should be implanted at reoperation is still matter of debate, the question between surgical replacement by homograft or bioprostheses valve haven't been solved.

B. Surgical prosthesis for failing right ventricular outflow tract

Cocomello and al. (4) found in their single center retrospective cohort of 209 operated tetralogy of Fallot, that homografts were superior in durability when compared to bioprosthesis for the treatment of pulmonary regurgitation. In opposition, Batlivala and al. (5) reported similar outcomes after a median follow-up of 4,4 years, between xenografts, mostly represented by Carpentier-Edwards ® (Edwards Life- sciences, Irvine, CA) and homografts in a cohort of 254 adolescents undergoing pulmonary valve replacement for either insufficiency or stenosis. Among the multiple types of surgical devices, bovine pericardial grafts showed the best profile compared to homograft and porcine valve, in a small series of 82 patients (6). This trend was also suggested by Cocomello and al. (4), that noticed, in their aforementioned study, a non-significant increased risk for reintervention and/or structural valve deterioration when comparing the subgroup of Carpentier Edwards Perimount ® (Edwards Lifesciences, Irvine, CA, USA) bovine pericardial valves with homografts, such findings were concordant with Batlivala and al. study (5). Additionally, it was noted that long-term anti-platelet therapy was associated with a lower risk of structural valvular deterioration. Recent data from the 258 patients retrospective cohort of Kwak and al. (7) compared two kinds of bioprosthesis and found, after a median follow up of 10,5 years, a significant increase in the rate of reoperation in the Carpentier-Edwards PERIMOUNT group (bovine pericardial valve) compared to the porcine valves (Hancock II ®), valve failure rates were 32,6% and 17,1% respectively. The authors suggested a prevalent phenotype of deterioration in the Carpentier-Edwards valves, consisting in thickened non-mobile leaflets presenting calcium deposits and fibrotic changes, resulting mostly in steno-insufficiency. In contrast, the Hancock II valves (Medtronic. Minneapolis, MN) were still

mobile but presented predominantly shrinkage or tearing, producing stenosis rather than regurgitation. This aforementioned finding was in opposition to previous studies in pulmonary or left-sided valves that describe the same proportion of valves explanted for steno-insufficiency. This deterioration phenotype was due to abundant pannus, gross calcifications, and a high burden of tears. It is worth noting that the rates of thrombus and endocarditis were higher among the porcine valves. Comparing the different evolutions of the same device, depending on its position, the authors suggested that the lower pressure in the right heart may give rise to a longer freedom from structural deterioration for bioprosthesis (9).

Even if surgical pulmonary valve replacement it is still the gold standard treatment it has to be kept in mind that it is associated with significant adverse events, ranging from 0,9 to 4% in mortality and 2,2 to 20,9% in terms of major complications (10), which impose a heavy burden on young adults, who already had a substantial hospital exposure in their childhood, and who require a quick rehabilitation to comply with social and professional activities.

C. Percutaneous approach in right ventricular outflow tract treatment

The development of percutaneous valve technology has introduced a paradigm shift in treatment possibilities. The report of Bonhoeffer et al. in 2000 (11) has paved the way for the development of the Melody® valve (Medtronic, Minneapolis, Minnesota, USA) (Figure 2) that has become the first device approved for prosthetic right ventricular outflow tract of diameter 16 to 22 mm. Different registries have subsequently shown favorable results in terms of efficiency (12), but they also have revealed an increased risk for infective endocarditis (13) related to the bovine jugular vein segment that composed the device (14).

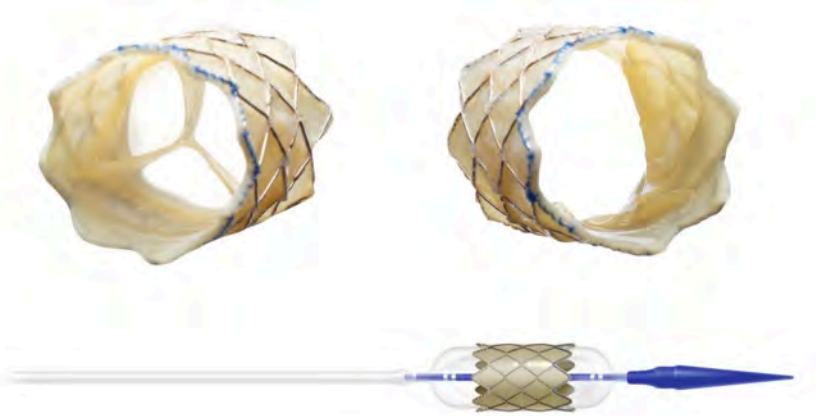


Figure 2. Medtronic Melody ® pulmonary valve (Medtronic Inc., MN, USA)

As an alternative Edwards SAPIEN ® (ES3; Edwards Lifesciences, Irvine, CA, USA) transcatheter heart valve, made of bovine pericardium, was first implanted in right conduit in 2006 (15) and subsequently different trials showed secure and effective parameters (16).

In 2016, the Edwards SAPIEN XT (Edwards Lifesciences, Irvine, CA, USA) (Figure 3) was approved by the Food and Drug Administration (FDA) to treat dysfunctional right ventricular outflow tract conduit (stenosis or regurgitation) with a diameter between 20 and 29 mm in patients with previous implantation of tube-grafts, allograft, bioprosthesis or transannular patch enlargement. The 3-year outcomes reported in the COMPASSION trial (17) were satisfactory, but little is known about long-term efficacy and safety.

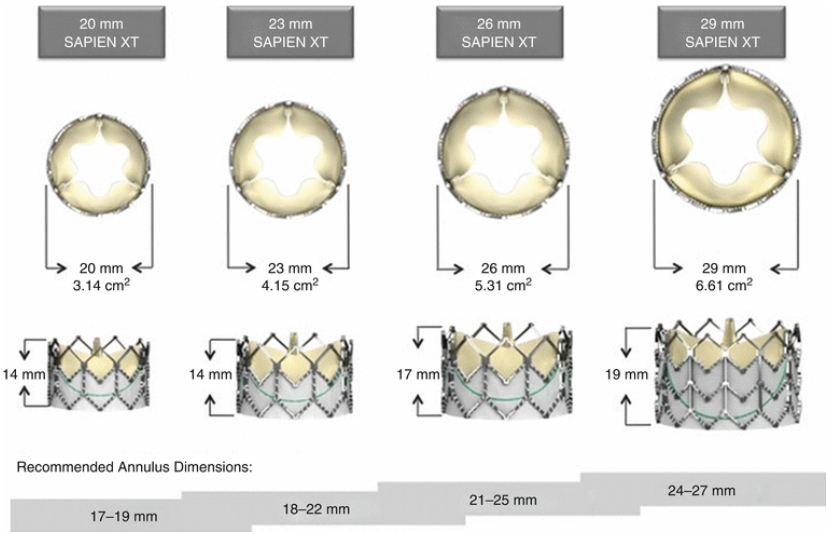


Figure 3. Edwards SAPIEN XT ® (ES3; Edwards Lifesciences, Irvine, CA, USA)

Controversial data are reported about morbidity and mortality when comparing surgery to transcatheter pulmonary valve replacement. Caughron and al. (18) didn't find any difference in mortality, cardiovascular readmission, or repeat PV intervention at 30 days, 1 year, or 3 years among 66 patients suffering from surgical bioprosthesis degeneration,

treated either with transcatheter pulmonary valve replacement (SAPIEN XT, 3 or Melody) (n=36) or repeat surgical pulmonary valve replacement (n=30).

Ying Zhou and al. (19) conducted a meta-analysis including 4364 patients (1,284 patients receiving TPVR and 3,080 undergoing SPVR) and compared outcomes for both techniques. A significant decrease in the length of hospital-stay, recurrent regurgitation, and mortality was found in the percutaneous group. Of note, patients in the surgical group presented a significant drop in postprocedural infective endocarditis rate.

Wen-Bin Ou-Yang and al. (20) confirmed the lower cost, the shorter hospitalization, and endotracheal intubation duration in a small retrospective study of 65 patients comparing Venus-P-valve and homografts. Therefore, this safe, effective and less invasive procedure has become the first line treatment. Initially restricted to specific indications it has been progressively extended to all kind of degenerative disease of the right outflow tract (conduits, homografts, bioprostheses, and transannular patch) (21). However it is not known whereas this treatment is still effective and beneficial for the patients after the first years.

Regarding the aortic position a recent registry, which included 34.7% patients treated with a balloon-expandable device, evidenced an incidence of severe structural deterioration below 1% after a long-term follow-up of 5.8 years (22).

D. Research issue

Because a transcatheter valve implantation in the pulmonary position involves a distinctive patient profile, a different implantation environment and specific hemodynamic conditions, a dedicated study is necessary to assess long-term performance.

We previously reported the one-year safety and efficacy of the Edwards SAPIEN valve in a multicenter prospective registry of pulmonary valve replacement (16). In the present study, we will assess the long-term (up to 7.5 years) clinical and structural outcomes of those patients that were treated with the Edwards SAPIEN XT transcatheter heart valve.

II. Methods

Between 2011 and 2016 participating centers in Paris (Hôpital Marie Lannelongue), Lille and Nantes included consecutively and prospectively all consecutive patients who underwent transcatheter right ventricular outflow tract treatment using the Edwards SAPIEN XT. Patients were either symptomatic, with Doppler mean gradients >35 mmHg and/or at least moderate pulmonary regurgitation, or asymptomatic, with significant regurgitant or stenotic right ventricular outflow tract, according to current recommendations (Figure 4) (21,23,24). To date no specific guidelines exist for transcatheter pulmonary valve replacement, therefore practices are extrapolation from the surgical indications (25).

Criteria	AHA [13]	ESC [11]	CCS [12]	Geva [6]
RVEDVi	≥Moderate	>160 mL/m^2	>170 mL/m^2	>150 mL/m^2 or Z-score >4 or RV/LV end-diastolic volume ratio >2
RVESVi	Not specified	Not specified	Not specified	>80 mL/m^2
RV function	≥Moderate RV dysfunction	Progressive RV dysfunction	≥Moderate RV dysfunction	RV EF <47%
RVOT obstruction[a]	PIG ≥50 mm Hg or RV/LV pressure ratio ≥0.7	PIG ≥80 mm Hg (4.3 m/s)	RV systolic pressure ≥2/3 systemic pressure	RV systolic pressure ≥2/3 systemic pressure
PR[a]	Severe	Severe	Free	≥Moderate (PRF ≥ 25%)
TR	≥Moderate	≥Moderate	"Important"	≥Moderate
QRS duration	Not specified	>180 msec	Not specified	>140 msec
Arrhythmia	Symptomatic or sustained AT or VT	Sustained AT or VT	AT or VT	Sustained tachyarrhythmia
Exercise cardiopulmonary function	Not specified	Objective decrease	Not specified	Not specified

AR, aortic regurgitation; AT, atrial tachycardia; EF, ejection fraction; LV, left ventricle; msec, milliseconds; PR, pulmonary regurgitation; PRF, pulmonary regurgitant fraction; RV, right ventricle; RVEDVi, right ventricular end diastolic volume indexed; RVESVi, right ventricular systolic volume indexed; RVOT, right ventricular outflow tract; VSD, ventricular septal defect; VT, ventricular tachycardia.

[a] AHA, ESC and CCS guidelines require the listed degree of PR or PS and one additional listed criterion, whereas the guidelines proposed by Geva suggest the specified degree of PR or PS plus 2 additional listed criteria (only one additional listed criteria is necessary if the initial repair was at age ≥3 years).

Figure 4. Summary of published guidelines for surgical valve replacement in asymptomatic patients. Extracted from Tretter and al., Int J Cardiol 2016

Were excluded pregnant women, patients less than 5 years-old, whom body weight was inferior to 30kg, or individuals with active infection. The main purposes of the study were to assess the late clinical events following the implantation of the Edwards SAPIEN XT valve and to evaluate device durability. As a consequence, patients for whom the procedure failed were excluded (n=3).

All were treated by SAPIEN XT valve implantation, using either the retroflex or novaflex delivery system. Procedures were performed through a femoral or jugular access under general anesthesia. The invasive conduit diameter sizing differed depending on the type of valve failure (figure 5).

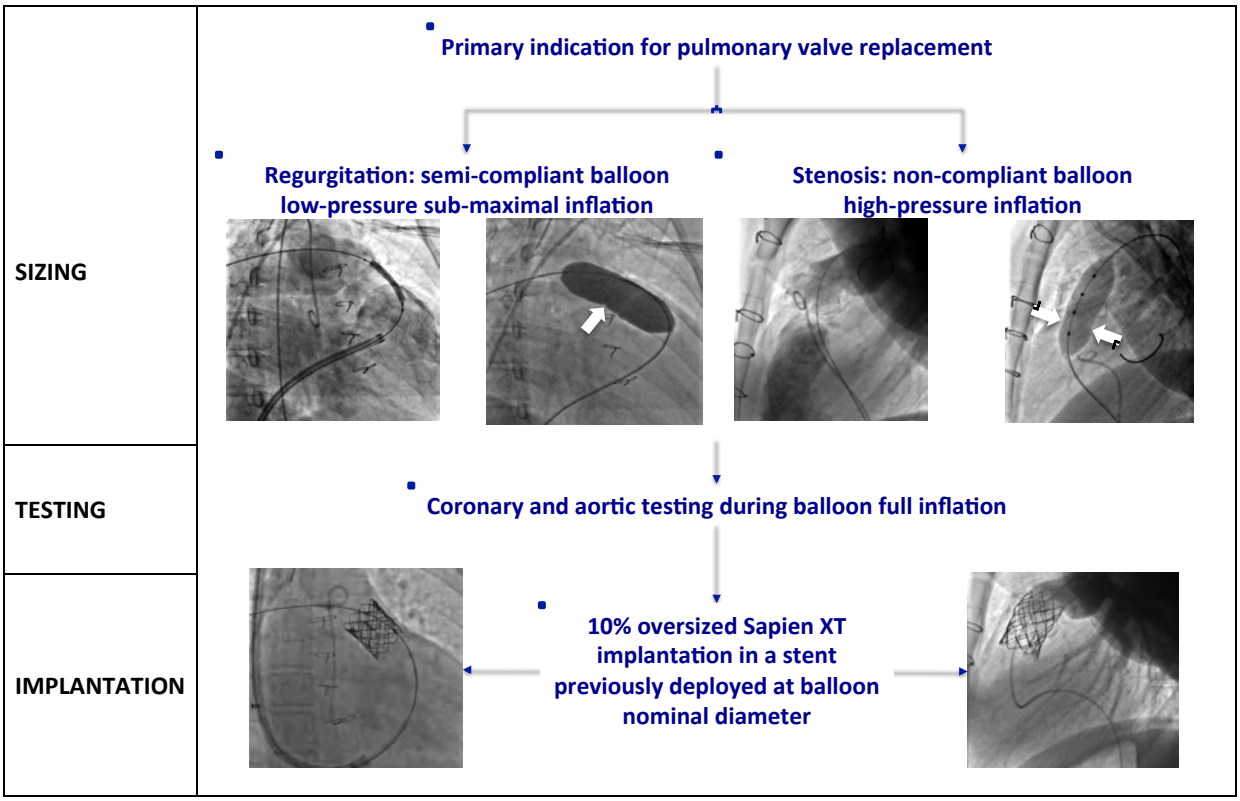


Figure 5. Invasive balloon conduit diameter sizing methodology depending on the primary indication for pulmonary valve replacement. The white arrow corresponds to the minimal residual indentation obtained after inflating the balloon at nominal diameter.

Regurgitant conduits generally display larger dimensions, therefore balloon-derived sizing starts with a semi-compliant balloon to determine the anchoring zone diameter, defined as the balloon diameter resulting in an indentation in the right ventricular outflow tract. The next step consists in performing the coronary compression testing with a semi-compliant balloon inflated at the intended diameter. Stenotic conduits were assessed after serial increasing dilations with non-compliant balloons until reaching the maximal expected diameter determined by: the nature of the conduit, the nominal diameter of the conduit and the minimal residual indentation obtained after several dilations, that constitutes the anchoring zone of the bioprosthesis.

Prestenting of the landing zone could be achieved concomitantly or in a differed manner. All patients received peri-interventional antibiotic prophylaxis with second-generation cephalosporin and were pre-treated with heparin (70 IU/kg).

Clinical and echocardiographic follow-up was carried out every 1 or 2 years depending on hospital modalities. The primary composite outcome was defined as the rate of all-cause mortality or transplant, infective endocarditis, and reintervention at the last follow-up available. Secondary outcomes included each individual component of the primary outcome, New York Heart Association (NYHA) clinical status, as well as parameters indicative of structural valve deterioration such as regurgitation (measured by spectral and color Doppler ultrasound) and stenosis (measured by Doppler maximal pulmonary gradient).

Informed consent was obtained from all patients and/or their legal guardians. The study was approved by French organizations (Commission Nationale de l'Informatique et des Libertés and Groupe Nantais d'Ethique dans le Domaine de la Santé).

Statistics

Continuous variables are expressed as mean with standard deviation or median with range. A subgroup analysis was performed for those patients requiring reintervention for recurrent right ventricular outflow tract obstruction.

The optimal cut-off value for the ratio of the largest implanted stent diameter to invasive balloon conduit diameter was established from the Receiver Operating Characteristic (ROC) curve.

Kaplan-Meier estimates were used to assess the probability of event occurrence. Survival curves were statistically compared using the log rank test.

Cox model were used to identify the risk factors for reintervention . Factors with a p-value < 0.1 were selected into the multivariable analysis. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using R version 3.6.3.

III. Results

A. Population

Among the 65 patients included into the French registry of pulmonary valve replacement between 2011 and 2016 after implantation of an Edwards SAPIEN XT valve, 3 were not considered for the present study because of a procedure failure, which included valve implantation failure (n = 1), device embolization (n = 1), or death during the procedure (n = 1), due to major hemoptysis and hemothorax (16).

Patient characteristics are summarized in Table 1. The median age of the population was 27 years (Figure 6) mostly represented by males (68%).

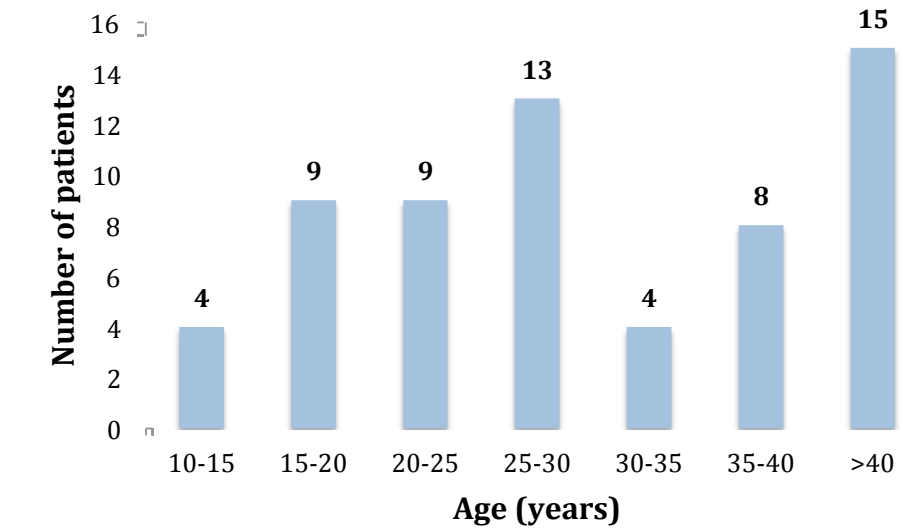


Figure 6. Distribution of patient ages at the time of intervention

Heart diseases were principally repaired conotroncal pathologies, concerning 41 of the 62 patients (66%), followed by 18 subjects (29%) with aortic valve diseases treated by Ross procedure. The indication for percutaneous pulmonary valve replacement was stenosis (37%), regurgitation (31%), or mixed lesion (31%).

Table 1. Patient characteristics at inclusion into the registry

	All patients	Patients with RVOT reintervention	Patients without RVOT reintervention
	(n = 62)	(n = 8)	(n = 54)
Age (years)	27 (12-76)	18 (12-34)	28.5 (13-76)
Male	42 (68)	6 (75)	36 (67)
Body mass index (kg/m^2)	23 ± 5	22.0 ± 5.8	23.4 ± 5.1
Weight (kg)	66 ± 16	62.1 ± 24.1	67.0 ± 15.1
Time since last surgery (years)	10 (6-16)	10.1 (6.3-10.6)	10.4 (5.4-17.6)
Heart disease			
Tetralogy of Fallot	26 (42)	2 (25)	24 (44)
Aortic valve diseases treated by Ross procedure*	18 (29)	3 (38)	15 (28)
Other conotruncal diseases†	9 (15)	2 (25)	7 (13)
Truncus arteriosus	6 (10)	1 (12)	5 (9)
Other	3 (5)	0 (0)	3 (6)
Number of previous cardiac surgeries			
0	1 (2)	0 (0)	1 (2)
1	14 (23)	0 (0)	14 (26)
2	23 (37)	3 (38)	20 (37)
3	18 (29)	3 (38)	15 (28)
4	6 (10)	2 (25)	4 (7)
Primary indication for pulmonary valve replacement			
Pulmonary regurgitation	19 (31)	1 (13)	18 (33)
Pulmonary stenosis	23 (37)	5 (63)	18 (33)
Mixed lesion	20 (32)	2 (25)	18 (33)

Values are median (range), mean ± standard deviation, or n (%).

*13 out of 18 cases of aortic valve diseases (72%) were congenital.

[†]41 out of 62 patients (66%) had a repaired conotroncal pathology.
RVOT: right ventricular outflow tract.

The specific features of the right ventricular outflow tract are reported in Table 2. Reconstruction was performed with a homograft (34%), a native conduit (27%), a bioprosthesis (23%), or a tube-graft (16%). Most tube-grafts (70%) were non-expandable woven synthetic polyester conduits and 60% were valved conduits.

Table 2. Right ventricular outflow tract (RVOT) features

	All patients	Patients with RVOT reintervention	Patients without RVOT reintervention
	(n = 62)	(n = 8)	(n = 54)
RVOT conduit type			
- Homograft	21 (34)	3 (38)	18 (33)
- Native (or noncircular patched RVOT)	17 (27)	1 (13)	16 (30)
- Bioprosthesis	14 (23)	0 (0)	14 (26)
- Tube-graft	10 (16)	4 (50)	6 (11)
o Expandable			
▪ Contegra	3	1	2
o Non expandable (woven synthetic polyester)			
▪ Hancock	3	1	2
▪ Intervascular valveless	1	1	0
▪ Gore-Tex valveless	1	0	1
▪ Hemashield valveless	1	0	1
▪ Non specified	1	1	0
Nominal RVOT conduit diameter range (mm)			
<20	12 (19)	4 (50)	8 (13)
20-23	20 (32)	3 (38)	17 (27)
23-26	13 (21)	0 (0)	13 (21)

≥26	8 (13)	1 (13)	7 (11)
Unknown	9 (15)	0	9 (15)
RVOT conduit diameter (mm)			
Nominal	21.7 ± 4 .0	19.3 ± 5	22.1 ± 3.6
Invasive	19.1 ± 3.6	16.1 ± 2	19.6 ± 3.6
Systolic peak-to-peak right ventricle to pulmonary artery gradient (mmHg)			
Before procedure	32.8 ± 18.7	48.8 ± 25.1	30.3 ± 16.5
After procedure	10.5 ± 6.8	14.6 ± 7.7	9.9 ± 9.9
Number of implanted stents			
0	1 (2)	0 (0)	1 (2)
1	50 (81)	8 (100)	42 (78)
2	8 (13)	0 (0)	8 (15)
3	2 (3)	0 (0)	2 (4)
4	1 (2)	0 (0)	1 (2)
Type of stents			
Intrastent Max LD EV3	39 (52)	7 (88)	32 (48)
Covered CP 8 Zigs	11 (15)	1 (13)	10 (15)
Bare CP 8 Zigs	16 (21)	0 (0)	16 (24)
Andrastent XXL	5 (7)	0 (0)	5 (7)
Palmaz	2 (3)	0 (0)	2 (3)
SINUS XL self-expandable	2 (3)	0 (0)	2 (3)
Stent diameter (mm)			
<20	1 (2)	1 (12)	0 (0)
20-23	24 (41)	3 (38)	21 (39)
23-26	33 (57)	4 (50)	29 (54)
≥26	3 (5)	0 (0)	3 (5)
Unknown	1 (2)	0 (0)	1 (2)
Valve diameter (mm)			
20	1 (2)	1 (13)	0 (0)
23	37 (60)	6 (75)	31 (57)

26	21 (34)	1 (13)	20 (37)
29	3 (4)	0 (0)	3 (6)
Diameter ratios			
Invasive to nominal	0.88 (0.77-0.99)	0.81 (0.76-0.88)	0.88 (0,77-1)
Largest implanted stent to nominal	1.07 ± 0.29	1.23 ± 0.37	1.04 ± 0.27
Largest implanted stent to invasive	1.21(1.09-1.40)	1.39 (1.33-1.47)	1.19 (1.09-1.33)

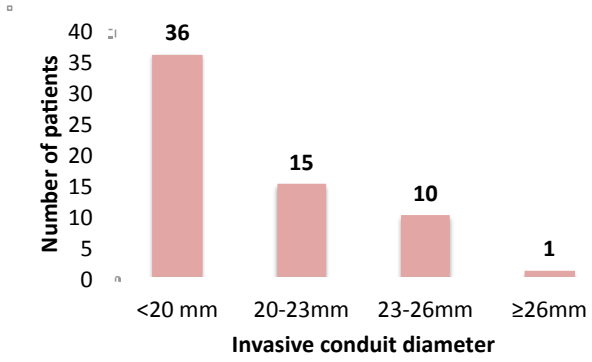
Values are median (range), mean ± standard deviation, or n (%).

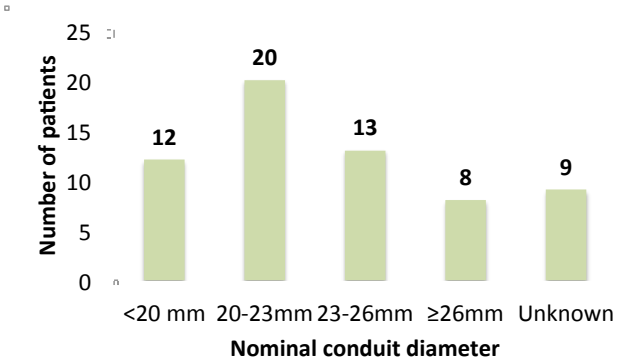
Tube grafts: Contegra® (Medtronic, Minneapolis, MN); Hancock® (Medtronic, Minneapolis, MN); Hemashield® (Maquet, Rastatt, Germany); Intervascular® (InterGard, La Ciotat, France).

Stents: intrastent Max LD EV3® (Medtronic, Minneapolis, MN, USA), CP 8 Zigs® (Numed, Inc, Hopkinton, NY, USA), Andrastent XXL (Andramed, Reutlingen, Germany), Palmaz (Johnson & Johnson, Cordis Division, Warren, NJ, USA), SINUS XL (Optimed, Ettlingen, Germany).

RVOT: right ventricular outflow tract.

At the time of the implantation, the mean right ventricular outflow tract diameter assessed invasively by balloon inflation was 19.1 ± 3.6 mm, resulting in a median nominal diameter to invasive conduit diameter ratio of 0.88 (range: 0.77-0.99). After the intervention, the maximal right ventricle to pulmonary artery gradient decreased from 32.7 ± 18.7 mmHg to 10.5 ± 6.8 mmHg. All patients but one had a pre-stenting with one (81%) or several stents. The main part of the implanted stents were intrastent Maxi LD EV3® (Medtronic, Minneapolis, MN) followed by bare and convered CP 8 Zigs stent® (Numed, Inc, Hopkinton, NY). The diameters used were mostly between 23 and 26mm, corresponding to a majority of SAPIEN XT 23mm implanted (Figure 7). Consequently the median ratio of the largest implanted stent diameter/invasive conduit diameter was 1,21 [1,09 ;1,40].





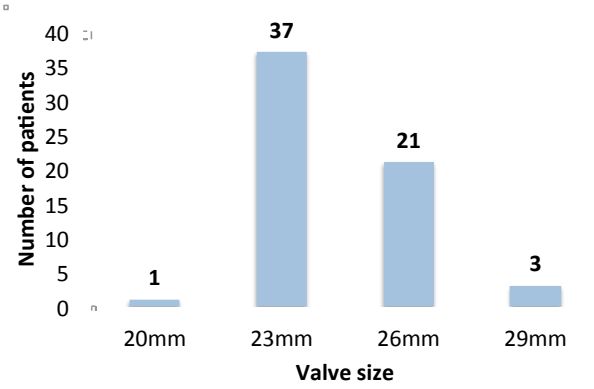


Figure 7. Distribution of invasive conduit diameter (top left), nominal conduit dimensions (top right), and Edwards SAPIEN XT valve sizes implanted (bottom)

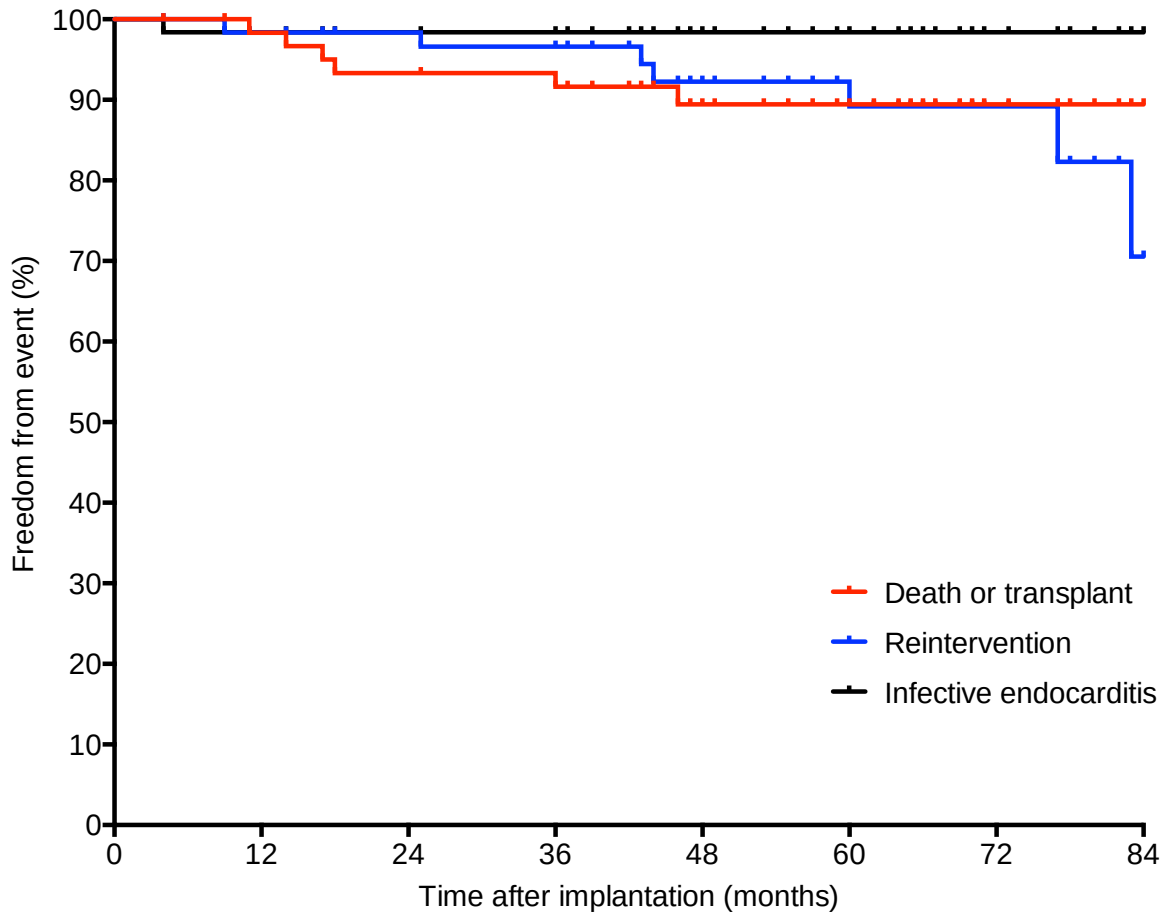
B. Primary outcome

After a mean follow-up of 55 ± 21 months, corresponding to 282 patient-years, the primary composite outcome defined as the rate of death or transplant, infective endocarditis, and reintervention reached 24.2%.

C. Secondary outcomes

1. Death and transplant

The incidence of death or transplant at 3 and 5 years was 8.4% (95% confidence interval (CI) 3.6-19%) and 10.6% (95% CI 4.9-22.1%), respectively (Figure 8).



Number of subjects at risk

Months	0	12	24	36	48	60	72	84
Death or transplant	62	59	56	55	40	30	14	6
Reintervention	62	59	56	55	40	30	14	6
Infective endocarditis	62	59	56	55	40	30	14	6

Figure 8. Kaplan-Meier estimates for the secondary outcomes: death or transplant, infective endocarditis, and reintervention.

Four patients (6.4%) died. Two of them had severe biventricular dysfunction and were not eligible for cardiac transplant. For these patients, percutaneous pulmonary valve replacement was a palliative treatment, they respectively died 11 and 17 months after the procedure. Sudden cardiac death was reported in a 39-year-old male patient with Down syndrome, 18 months after pulmonary valve implantation for severe pulmonary regurgitation complicating a patch-repaired tetralogy of Fallot with reduced left

ventricular ejection fraction. A fourth patient died at age 79 from rapid deterioration of a neurodegenerative disease, 36 months after valve implantation for an isolated unoperated pulmonary stenosis.

Two patients (3.2%) underwent cardiac transplantation, both were young adults with repaired tetralogy of Fallot.

2. Infective endocarditis

At 5 years, freedom from endocarditis was 98.4% (95% CI 89.1-99.8%) (Figure 8). One case (1.6%) of infective endocarditis was reported during follow-up that was caused by multi-resistant staphylococcus epidermidis resulting in the device being explanted 4 months after implantation.

3. Reintervention

The incidence of reintervention at 3 and 5 years was 3.4% (95% CI 0.9-12.9%) and 11% (95% CI 4.6-25.2%), respectively (Figure 8). Eight patients (12.9%) had a reintervention, which was exclusively due to recurrent right ventricular outflow tract obstruction (Figure 9) with no stent fracture, and required either surgical valve replacement (n = 2), balloon dilation (n = 1) or valve-in-valve procedure (n = 5). Of note, one patient (Patient 6 on Figure 9) was operated again less than one year after the reintervention because of a partial obstruction of the right pulmonary artery, in addition to a right ventricular outflow tract residual stenosis.

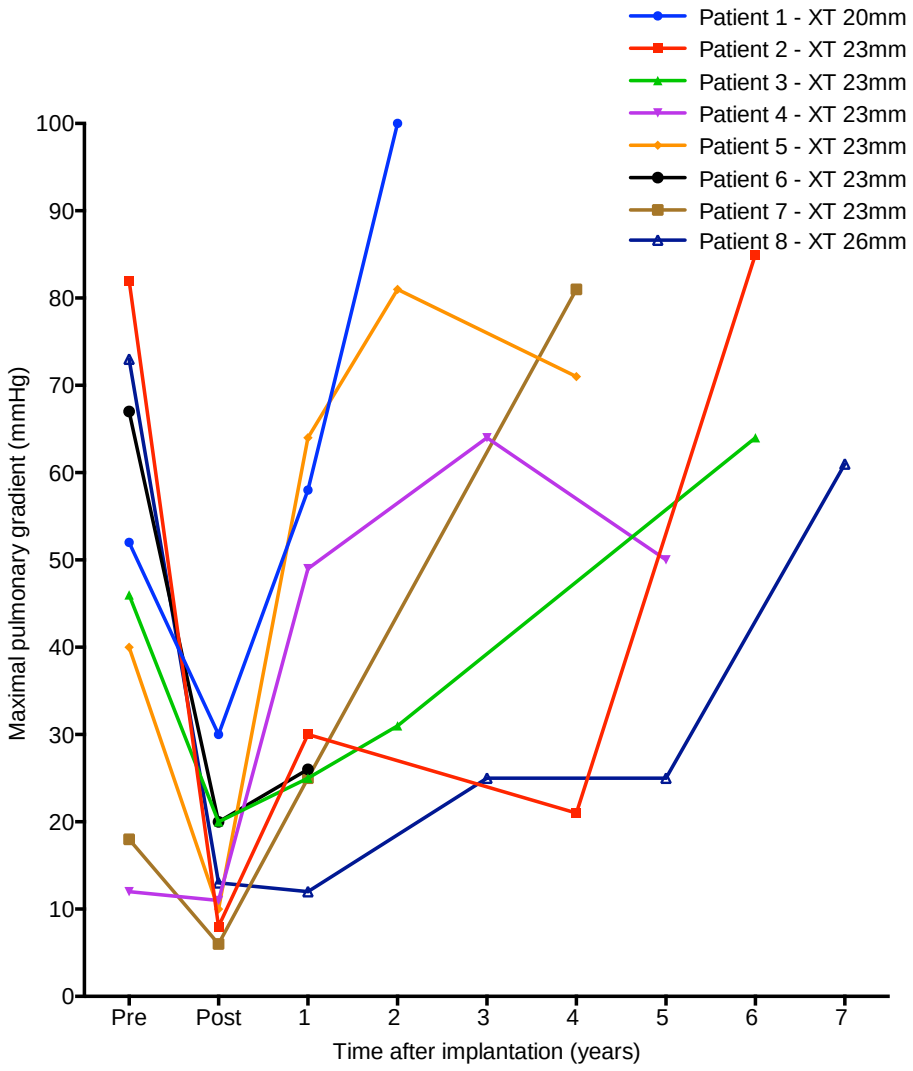


Figure 9. Individual maximal gradients rise of the eight patients presenting recurrent right ventricular outflow tract obstruction Individual maximal pulmonary gradient rise for the 8 patients presenting recurrent right ventricular outflow tract obstruction. Values are also presented pre-procedure (Pre) and post-procedure (Post).

4. Other secondary outcomes

Before the intervention, most patients (85%) were in New York Heart Association (NYHA) functional class II to IV, but after the intervention, most were in NYHA class I (80%) and they remained in class I (79%) at the late follow-up (Figure 10).

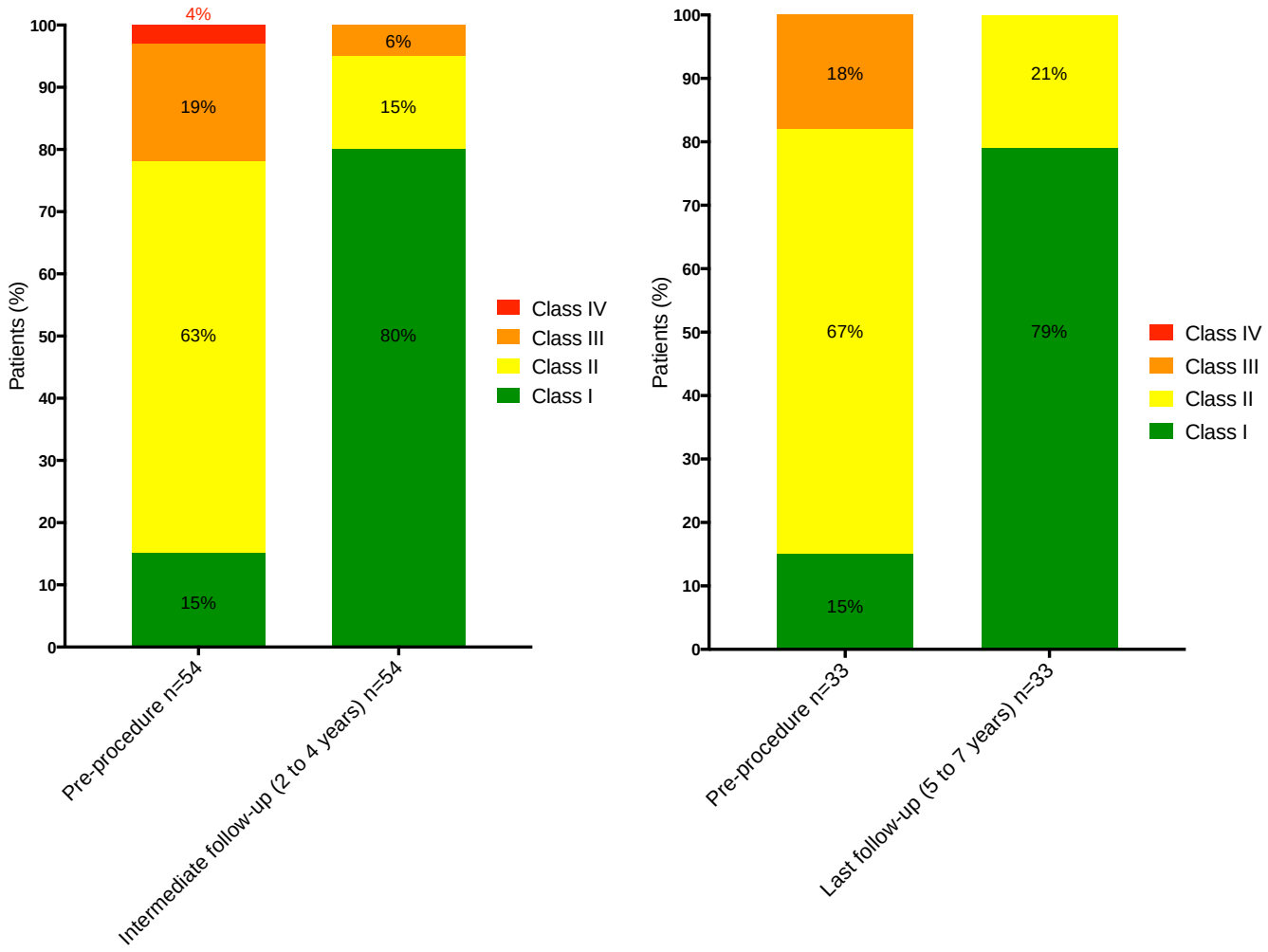


Figure 10. New York Heart Association (NYHA) clinical status evolution from pre-procedure to intermediate (left) and last (right) follow-up for patients with data available before the procedure and at each respective follow-up.

The cohort remained free from significant valvular insufficiency (defined as grade 2 and above) during the follow-up (Figure 11).

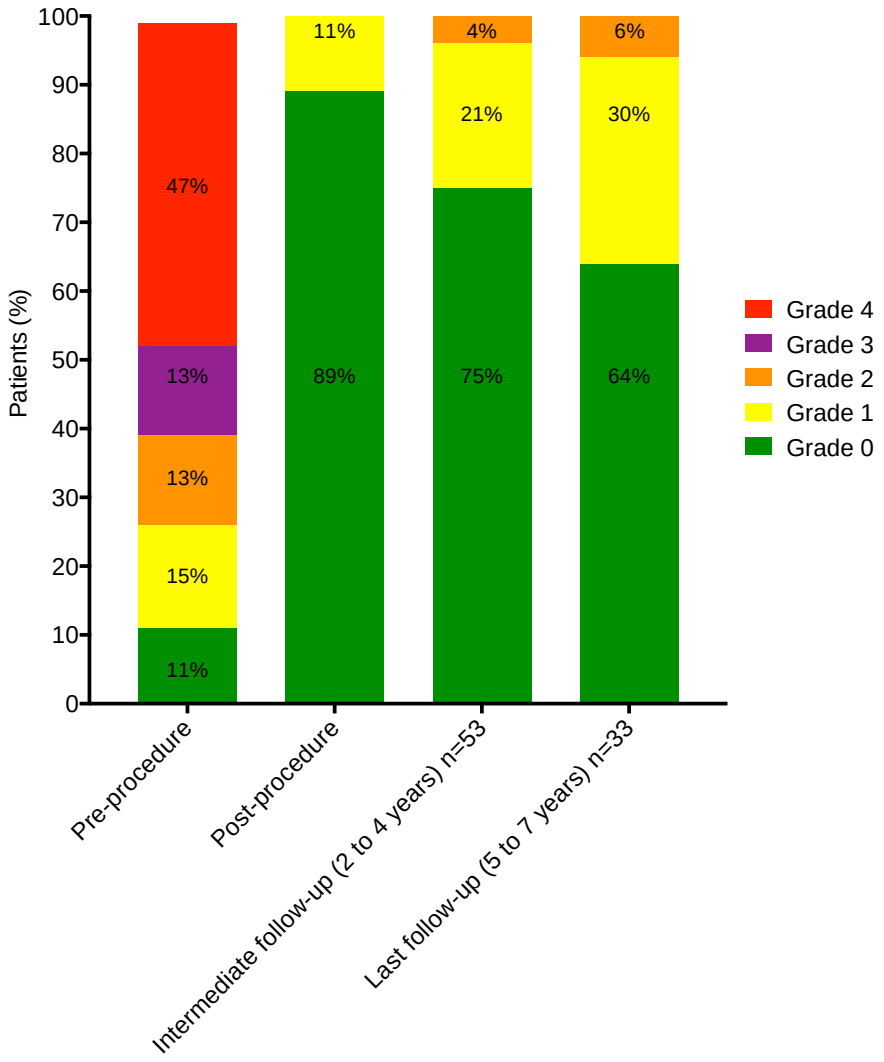


Figure 11. Pulmonary regurgitation evolution over time

The device efficiently reduced the obstruction especially when it was important to start with (Figure 12). The mean peak to peak gradient decrease was 22 ± 12 mmHg after the procedure, and this level was maintained throughout the follow-up. The median value of the maximal pulmonary gradient at last follow-up was 28 mmHg (range: 19-34 mmHg). However, evolution with time depended on the initial indication for valvular replacement (Figure 12). Generally, patients treated for pulmonary regurgitation (31%) preserved low gradients (median: 19 mmHg; range: 12-28 mmHg), whereas patients with mixed or stenotic lesions had higher gradients (median: 31 mmHg; range: 26-41 mmHg).

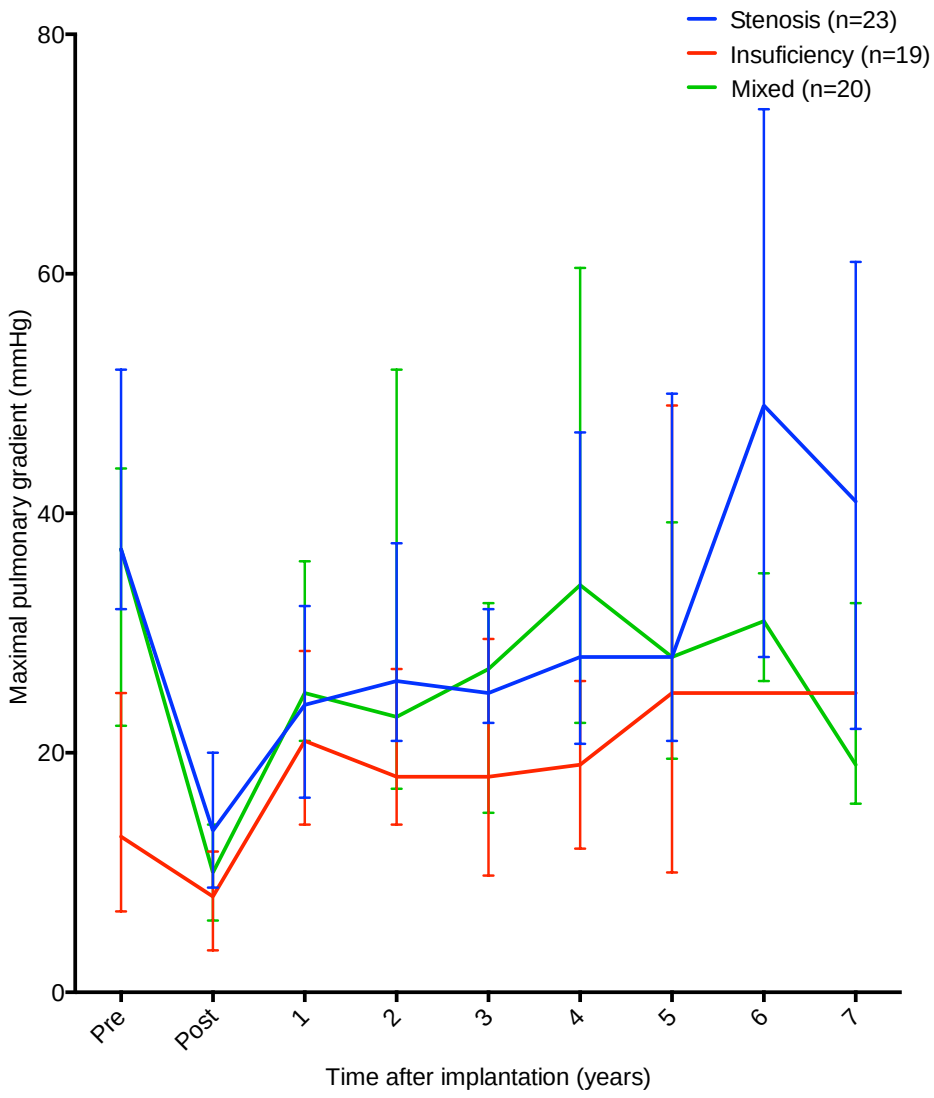


Figure 12. Maximal pulmonary gradient evolution over time stratified according to primary indication for implantation. Values are also presented pre-procedure (Pre) and post-procedure (Post).

5. Patients requiring reintervention - subgroup analysis

The specific features of the patients with (n = 8) and without (n = 54) recurrent right ventricular outflow tract obstruction are compared in Table 1 and 2. Four of these patients were among the first 15 patients to undergo the procedure at one center. Patients with recurrent obstruction were predominantly males (n = 6 out of 8), and they were younger than those without reintervention (median: 18 versus 28 years old). They had congenital aortic stenosis (n = 3), tetralogy of Fallot (n = 2), other conotruncal diseases (n = 2) or truncus arteriosus (n = 1) with no relevant associated comorbidity (renal or respiratory diseases, diabetes). The main indication for the first intervention was stenosis in 5 cases (63% versus 33% for patients without reintervention), whereas

regurgitation, occurring in 1 patient, was less frequent (13% versus 33% for patients without reintervention). The rate of patients treated with a tube-graft was higher in the group with reintervention (50% versus 11%). In addition, for these patients, 50% of the conduits had a nominal diameter of 20 mm or less, that was measured invasively to be 16.1 ± 2 mm. This resulted in higher peak to peak gradients (48.8 ± 25.1 mmHg versus 30.3 ± 16.5 mmHg) before the intervention. Nevertheless, the stent diameter range did not differ between groups, whereas the valve dimensions did, with the 23-mm valves being more prevalent in the reintervention group (75% versus 57%). In the same manner, it is worth to notice that all the patients received a single stent in the reintervention group (versus 78% in the group without reintervention). Finally, patients with reintervention had a greater ratio of largest implanted stent diameter to invasive balloon conduit diameter (1.39 versus 1.19, reflecting the difficult management of adequate sizing in that particular population.

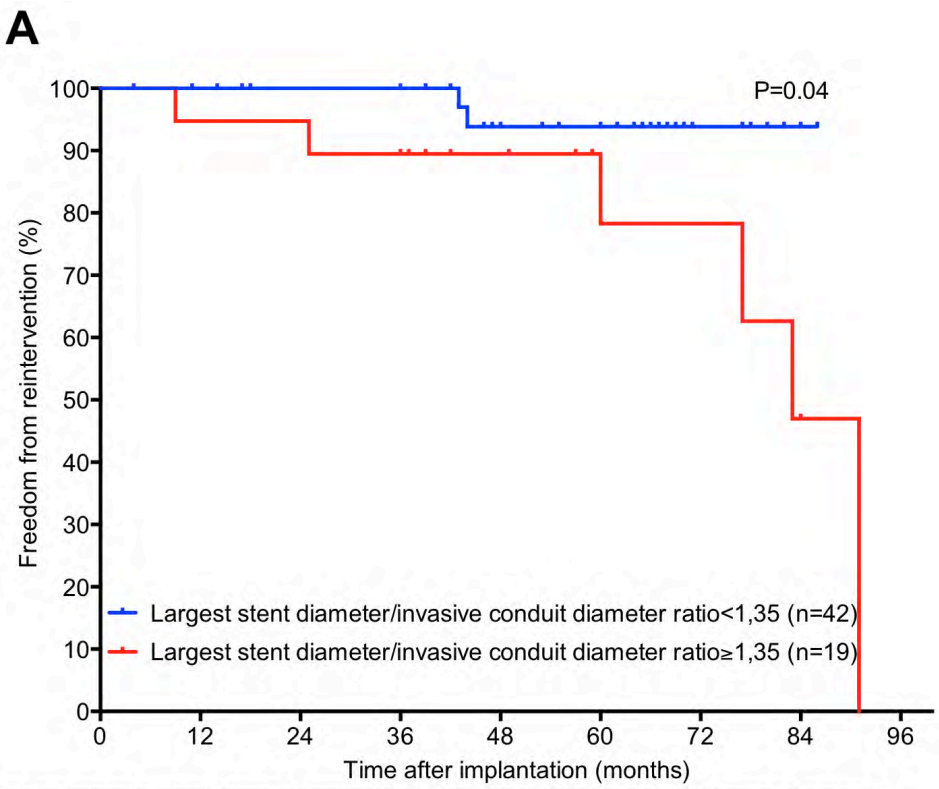
The mean time of follow up was 54 ± 29 months in the reintervention group and 55 ± 20 months in the no-reintervention group.

In univariate Cox regression, age 18 years old or less, use of a tube-graft, a nominal diameter of 18 mm or less, an invasive diameter of 16 mm or less, a post-implantation peak to peak gradient of 20 mmHg or more and a ratio of the largest implanted stent diameter to invasive balloon conduit diameter of 1.35 or more were associated with increased risk for reintervention for recurrent right ventricular outflow tract obstruction (Table 3). A multivariable regression identified age 18 years old or less as the only independent predictive factor for reintervention (risk ratio: 11.8; 95% CI: 1.13-122.7; p = 0.039).

Table 3: Factors associated with reintervention for recurrent right ventricular outflow tract obstruction in univariable Cox regression

	Risk Ratio	95% CI	p-value
≤ 18 years old	24.3	2.7-219.8	0.0045
Tube graft	5.5	5.5-25.1	0.027
Nominal diameter ≤ 18 mm	5.4	1.2-24.3	0.027
Invasive diameter ≤ 16 mm	7.9	1.5-41.3	0.014
Pre-implantation peak to peak gradient ≥ 40 mmHg	32.1	0.83-1242	0.063
Post-implantation peak to peak gradient ≥ 20 mmHg	5.0	1.1-22.5	0.038
Ratio of the largest implanted stent diameter to invasive balloon conduit diameter ≥ 1.35	5.9	1.1-30.6	0.035

Among all parameters potentially associated with the specific outcome of reintervention for obstruction, the ratio of stent diameter to invasive conduit balloon diameter appears as the unique modifiable variable that could help guide the adequate sizing of the stent used for pre-stenting, and therefore of the valve to be implanted. Indeed, for those patients with a diameter ratio < 1.35, the occurrence of reintervention for obstruction was decreased ($p = 0.04$) and the maximal pulmonary gradient tended to be lower at all time points during follow-up (Figure 13).



Months	0	12	24	36	48	60	72	84	91
Ratio<1,35	42	41	38	37	28	21	8	2	0
Ratio≥1,35	19	19	19	17	13	8	8	3	1

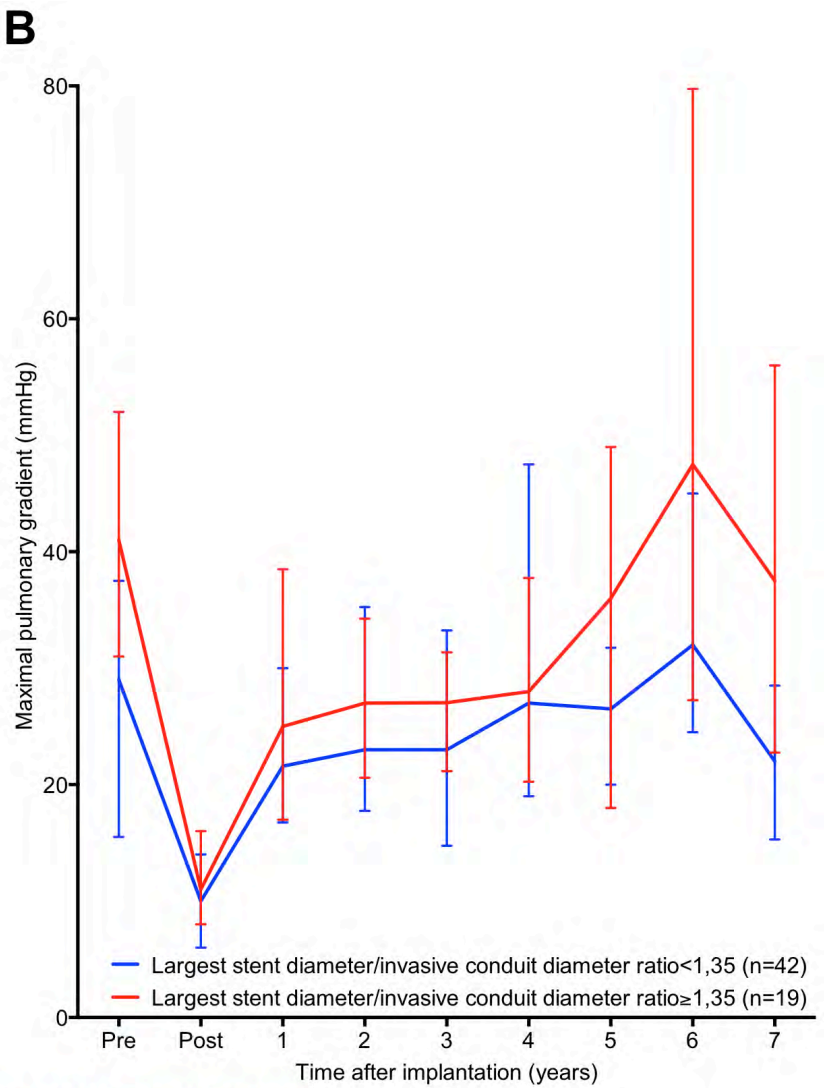


Figure 1. A. Kaplan-Meier estimates for reintervention for right ventricular outflow tract obstruction stratified according to the value of the ratio of the largest implanted stent diameter to invasive balloon conduit diameter. B. Maximal pulmonary gradient evolution over time stratified according to the value of the ratio of the largest implanted stent diameter to invasive balloon conduit diameter. Values are also presented pre-procedure (Pre) and post-procedure (Post).

IV. Discussion

This multicenter prospective study, including 62 patients with congenital heart disease, is the first to report long-term follow-up (up to 7.5 years) after implantation of an Edwards SAPIEN XT valve in the pulmonary position. The primary composite outcome of death or transplant, infective endocarditis and reintervention was 24% (9.6% for mortality or transplant, 1.6% for infective endocarditis and 12.9% for reintervention) after a mean follow-up of 55 ± 21 months. This study evidenced the reliability of the valve over time, which was associated with improved clinical status, no major concern for infective endocarditis, and no post-implantation device-related death, thus confirming previously published short-term results (16). A subset of patients was identified to have an increased risk for reintervention caused exclusively by recurrent RVOT obstruction in the setting of valves that are implanted in small conduits in a disproportionate manner, most of the time in young patients.

Important insights are provided into structural valvular integrity over time. No relevant pulmonary regurgitation was reported after long-term follow-up. Stenotic deterioration was the only cause for reintervention and concerned 13% patients. Previous registries, which have collected long-term follow-up data on the Melody® valve (27), have similarly reported no major recurrent valvular insufficiency. The first reports have detected a high incidence of endocarditis (up to 10% (12)), which could contribute to the increased rates of reintervention, ranging from 11% (12) to 22% (26). At 5 years, the incidence of infective endocarditis in our study was only 1.6%. The only case we reported was caused by multi-resistant staphylococcus epidermidis requiring device removal 4 months after implantation. Nosocomial infection was suspected given the pathogenic germ and the short symptom onset (3 months after implantation), suggesting that the therapeutic procedure itself rather than the device was the origin of the infection.

The low occurrence of reinterventions in our study does not allow to identify clear risk factors but several specific features can be outlined for the patient population at risk. New onset of obstruction was more frequent in young males (75%), implanted with a tube-graft (50%), mostly unexpandable. These patients presented with a high post-implant transpulmonary gradient in the setting of narrowed nominal and invasive

diameters, with a resultant stent diameter to invasive conduit balloon diameter ratio equal or beyond 1.35.

RVOT dysfunction can be safely treated with the Melody® valve even when the conduit diameter is smaller than 17 mm (27), but this is not transposable to the Edwards SAPIEN XT valves of our study, which were at least 23 mm in diameter (except for one 20-mm valve). In fact, the stent diameter to invasive conduit balloon diameter ratio is representative of the risk of mismatch between the valve annulus and the bioprosthesis. It has also been associated with the well-known risks of stent fracture and acute recoil (28), as it has been documented in the aortic position for a prosthesis/annulus tomography diameter ratio over 1,04 (or 1,15 in transthoracic echocardiogram). Because of its elasticity, the cobalt chromium stent of the SAPIEN XT valve (29) may be particularly prone to plastic deformations under chronic cyclic mechanical stresses. Even if pre-stenting may attenuate the forces directly applied onto the device framework, partial distortion may occur. In our study, in contrast with the majority of large trials (26,27,30), the most frequently used endovascular prosthesis was the Intrastent Max LD EV3 (Medtronic, Minneapolis, Minnesota, USA), a laser-cut, stainless steel tube, with a unique open-cell design. Although this stent is currently broadly used, initial reports raised concerns about its use in conditions of oversizing and external compression, mainly because of its non-bridged cells, which are more prone to asymmetric expansion due to decreased radial force (31,32). Such conditions are likely to be present in the setting of stenotic right ventricular outflow and to be exacerbated in the context of pre-stenting mismatch. Despite the statistically non significant difference the Prospective North American and European Melody Valve Trials (33) observed a 20,5 % (n=9) rate of reinterventions at 2-years among the patients with a stentless conduit implanted of a single EV3, compared to 4,5% for the Palmaz XL, a closed-cell design stent.

The question about late recoil remains unanswered, but could be of major interest considering the high prevalence, in the pulmonary position, of heavily calcified conduits of restricted dimensions (27). Moreover, the oval shape of the pulmonary annulus (34) may be of particular importance considering that the assessed bioprostheses have been designed for optimal performance in circular aortic ring. Therefore, the resultant stiff and asymmetrical landing zone associated with bioprosthesis plastic deformations under

chronic cyclic mechanical stresses could engender an elliptical or underexpanded deployment, compromising leaflet durability (35).

In our study, the stent diameter to invasive conduit balloon diameter ratio was identified as a predictive factor for reintervention but it could also be an indicator for excessive dilation when pre-stenting. It is known that the conduit diameter may change over time (36) and be expanded beyond the nominal diameter. The recommendation following the US IDE trial (30) was to avoid exceeding 110% of the original conduit diameter at the time of pre-dilation. On the other hand, doing so in small conduits has been associated with high rates of stent fracture (33).

We can then formulate the hypothesis that given the wide range of diameters proposed for the SAPIEN XT valves, the likelihood of size mismatch between the landing zone and the device is increased in small conduits. However, keeping a low stent diameter to invasive conduit balloon diameter ratio, while relieving efficiently the obstruction, may limit the risk of reintervention. Further studies are required to confirm the hypothesis of mismatch-induced recoil and to assess the feasibility of multiple stenting or use of close-cell devices to counterbalance this adverse effect.

The strength of this study relies on a multicenter and prospective design. Its originality is based on the long-term follow-up of the largest cohort ever treated with the Edwards SAPIEN XT valve, a device that has only recently been approved for implantation in the pulmonary position. It provides relevant findings that will be useful for the design of future clinical trials but it has several limitations. Inclusion was limited to those patients receiving an Edwards SAPIEN XT valve, with no sample size calculation, which limited the interpretation of subgroup analyses. Despite strict inclusion criteria, the population was heterogeneous, and this in turn prevented any adjustment for confounding factors. We had no choice but to use the maximum pulmonary gradient as the main parameter for the assessment of valve function over time, albeit it is known to consistently overestimate the peak to peak gradient (37). Another limitation comes from the lack of reproducibility of invasive conduit measurements caused by the pulmonary annulus not being circular and by intra and interobserver variability. The aim of this clinical assay was solely descriptive and the results should only be considered as hypothesis generating. Moreover, we excluded from our analyses the procedures that were

unsuccessful in terms of valve implantation. Even if those cases represented only 5% of the entire cohort, this limitation deserves to be kept in mind.

V. Context and perspectives

A. Intervention timing

1. Focus on the right ventricle

For decades we have considered that pulmonary replacement timing was determined by clinical (38) and imaging assessment (39) suggesting right ventricular dysfunction. Nonetheless Cavalcanti and al. (40) showed in their meta-analysis including 3118 patients operated for pulmonary valve replacement after a repaired tetralogy of Fallot, that when treated late, patients with large pre-operative volumes presented a favorable remodeling of right chambers but without a clinical improvement in the same extent. It has been advanced that after the restoration of a competent valvular function, ventricular remodeling was self-limited beyond a certain degree of dilation, 160 to 170mL/m2 for the indexed right ventricular end-diastolic volume (RVEDVi) (39,41) and 82mL/m2 for the indexed right ventricular end-systolic volume (RVESVi)(42). Moreover, imaging identifies prognostic factors, patients presenting a RVESVi greater than 95mL/m2 experience significantly more right ventricular dilation, and decline in ejection fraction. Both factors being associated with adverse clinical events (43). Ling Heng and al. (42) demonstrated in 2017 in their 57 patients single center prospective study, that right ventricular remodelling after surgical pulmonary valve replacement was mostly achieved within the 6 days after implantation of a competent pulmonary valve, with a 32% reduction in the right ventricular end-diastolic volume that was maintained at 3 years. Interestingly end-systolic volume diminution was 23% in the few days following surgery and reached 32% at the midterm follow-up. The predominant early changes in right ventricular volumes suggest a direct effect of the resolution of the volume overload, whereas the midterm remodeling is consistent with a mild improvement of the ejection fraction and possibly biological processes, whose role seem however rudimentary.

Meanwhile multiple sources put forward the hypothesis that dilation or failure of the right heart predicted bad prognosis, as iterative cardiac surgeries does (44). However some studies have shown that mild right ventricular dilation remains stable after an average follow-up of 3 years, among young adults presenting a pure pulmonary regurgitation following a repaired tetralogy of Fallot (45). Albeit at higher risk, the rate of adverse

events in that population is still low, notably since the implementation of the modern single-stage corrective repair, leading to a 40-year survival of 90%, and a constant rate of reoperation around 0,8%/year (46). Based on those findings several authors claim to reinforce the watchful attitude strategy in asymptomatic patients, instead of performing early pulmonary replacement founded on chamber volume measures, and without a clear established benefit on hard clinical outcomes (47).

Although valve implantation is effective in restoring favorable cardiovascular hemodynamics it may also induce adverse events associated with the index procedure, but also related to the device itself, exposing to the risk of deterioration or infective endocarditis resulting in reoperation and potential morbimortality (48).

However, recent observational trials suggest that an older age at reintervention as well as a right ventricular dysfunction or hypertrophy are associated with adverse events (49,50) (figure 14). Considering the hypertrophy as the only reversible risk factor, it may be considered to encourage a close follow-up during the third decade of life, and proceed to valve replacement previously to the occurrence of irrecoverable sequelae induced by longstanding exposure to hemodynamic disorders in relation to the underlying right ventricular outflow tract disease.

At the same time, alternative pathophysiological concepts beyond the hemodynamic theory have emerged. As more than 90% of the patients develop a right ventricular bundle branch block after tetralogy of Fallot surgery, the electromechanical dyssynchrony theory appeared to be a promising postulate to gain insight into the mechanisms underlying the right ventricular dysfunction. Preliminary studies incorporating a computer modeling found that right ventricular dysfunction is more related to the QRS duration, than to the pulmonary regurgitation fraction. This discovery could explain the lack of improvement in cardiopulmonary testing following pulmonary valve replacement in chronically volume loaded-right ventricle, in opposition to the effectiveness encounter for the pressure overload phenotype (51). Hence, Lumens and al. promote the possible benefits of right resynchronisation to decrease the mechanical delays between both ventricles, and therefore improve exercise capacity (52).

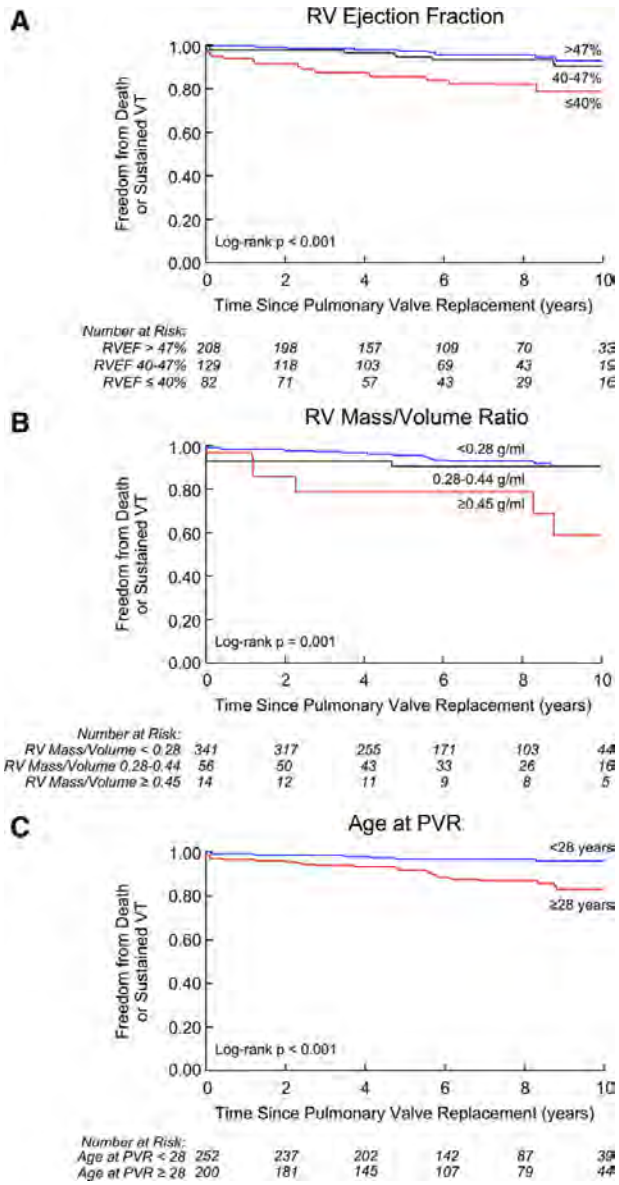


Figure 13. Kaplan-Meier analysis of freedom from death and sustained VT after pulmonary valve replacement, stratified by different threshold values of key predictors. Extracted from Geva and al., Circulation, 2018

2. Focus on the sudden cardiac death

Late cardiac arrests, suspected to be ventricular arrhythmias, have been observed since the beginning of tetralogy of Fallot surgical repair. This finding was secondly documented and confirmed in multiple observational trials (53). The incidence of sudden cardiac death is estimated to be around 0,2%/year 10 years after correction, with a continuous increase overtime (0,5%/year 30 years after correction) (46,54), representing approximately 35% of all mortality in that pathology (55). Arrhythmia is the main

mechanism suspected to be causal for this increase lethality, although conduction disturbances could be considered in specific settings (56). In a retrospective 793 patients cohort of repaired tetralogy of Fallot, followed up during a mean time of 21,1 years, it was found that the rate of sustained ventricular tachycardia reached 11,9% while sudden cardiac death affected 8,3% of the population (53). The authors identified for both events, common risk factors, represented by QRS duration over 180ms and its dynamic progressive lengthening during the follow-up, as well as the presence of a moderate to severe pulmonary regurgitation or an outflow tract patch. Further studies identified several additional predictors of cardiac arrest such as the older age at repair, the preoperative NYHA status, strongly interrelated to the severity of hypoxia, that may ultimately favor the occurrence of myocardial fibrosis (54,55,57).

It is hypothesized that the pulmonary regurgitation is the main phenomenon responsible for all the electro-mechanical pattern leading to life threatening arrhythmia. By inducing a chronic volume overload right chambers expand, engendering a concomitant lengthening of ventricular depolarization that prolong even more the QRS duration, usually already enlarged due to surgical injury on the myocardium and the right bundle branch. This late remodeling may be better reflected by QRS rates of change rather than the absolute value of the complex duration. Finally, this progressive ventricular enlargement associated with the ventriculotomy scar and patch provides the electrophysiological heterogeneity substrate necessary to the genesis of reentry-induced ventricular tachycardia (58). Valvular insufficiency is not the unique underlying disease exposing to the risk of rhythm disturbance. Right ventricular hypertension, residual outflow tract obstruction, right ventricular hypertrophy and dysfunction have also been linked to sudden cardiac death occurrence (49,57,59).

Even if an association was found in multiple observational trials, the causal effect of the hemodynamic consequences of the pulmonary valve dysfunction remains to be proved. In the same extent uncertainty persists regarding how pulmonary valve replacement could reverse the pathophysiological process leading to rhythmic susceptibility.

Burchill and al. (60) argue that QRS duration, being the main marker of the risk of sudden cardiac death in repaired tetralogy of Fallot (38), correlates with right ventricular dilation (58). Therefore it is tempting to think about normalization of right ventricular

volumes as a treatment goal to protect from ventricular tachycardia. In fact, it was shown, in a cohort of 133 patients that had a pulmonary valve replacement, a significant shortening of the complexes after 3 years, that was associated with a decrease in right chambers size (61). According to that, Geva and al. (49) noticed in an observational investigation of 452 repaired tetralogy of Fallot that an older age and signs of advanced right ventricular remodeling (hypertrophy/dysfunction) at valve replacement were predictive of death and ventricular tachycardia after intervention. This is in keeping with recent studies suggesting a deleterious effect of a late timing valve surgery, as shown by the significant increase mortality in patients undergoing the first time pulmonary intervention after 35 years-old (50). However, pulmonary valve replacement hasn't been always found as a protective factor against adverse events. Bokma and al., reported about 977 repaired Tetralogy of Fallot patients from the INDICATOR registry, assessing, through a propensity score, the freedom of clinical outcomes between patients that underwent valvular surgery and the patients that did not. The study included mostly young subjects (26±15 years) followed up during an average of 5,3 years, and didn't find significant reduction of events among the participants receiving a pulmonary valve replacement (62).

Because most of the available data are provided by studies evaluating the surgical valve replacement in repaired tetralogy of Fallot subjects, the extrapolation to all the rest of the etiologies of right ventricular outflow tract dysfunction must be prudent.

3. Perspectives

From those observations emanated the hypothesis that an earlier mini-invasive intervention, such as the percutaneous approach, could break the deleterious crosstalk between dysfunctional outflow tract and right ventricle function, before the occurrence of irrecoverable consequences. The implementation of this therapeutic strategy cannot be sustainable without demonstrating the durability and long term safety of such devices. As the Melody valves have been related to high rates of infective endocarditis (13), Edwards balloon expandable bioprosthesis appeared then to be the most reliable technique addressed to young and active patients (63).

Concerning valve performance, our study provides reassuring data with no significant regurgitation and global stability of transvalvular gradients. Even though longer follow up

may show structural valvular degeneration, valve in valve interventions are still feasible, secure and effective to restore a satisfactory function. Nevertheless further studies are needed to investigate whether it correlates with beneficial clinical outcomes.

B. Adjunctive therapies

1. Anti-thrombotic therapy

a) Structural valvular degeneration

Egbe and al. demonstrated the effect of the presence of hemodynamically significant thrombosis, on surgical bioprosthesis rapid deterioration, and occurrence of clinical events if left untreated (64). However, it concerned almost exclusively left sided valves, and more than 90% of the participants were already under antiplatelet therapy. Warfarin with a therapeutic INR was a protective factor, as well as the pericardial valve tissue compared to the porcine implants.

Concordant data are also reported for the percutaneous valves implanted in the aortic position. Hansson and al., found, in a prospective cohort of 460 patients implanted with SAPIEN valves XT or 3, that 7% of the participants presented valve thrombosis in multidetector computed tomography, of which 82% were asymptomatic. Interestingly, vitamin K antagonist therapy was once again significantly associated with the absence of hypoattenuated leaflet thickening (65). This finding gave insights into the detrimental effect advanced by Del Trigo and al., of the lack of anticoagulant therapy post-transcatheter aortic valve replacement (TAVR) in the development of device hemodynamic deterioration (66). From the hypothesis that infraclinical valve thrombosis predisposes to early structural valve deterioration, different randomized clinical trials sought to assess the benefits of a systematic anticoagulation therapy following TAVR. Of note, the GALILEO trial (Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) that evaluated a single dose of rivaroxaban 10mg, was interrupted due to an increased mortality and bleeding events in the study treatment arm (67). It is however noteworthy to mention the four-dimensional computed tomography substudy, that documented the efficiency of the rivaroxaban in preventing subclinical leaflet motion abnormalities (68).

After surgical pulmonary valve replacement, the use of anti-platelet therapy appears to lower the risk of reintervention or structural valve deterioration (4) (Figure 15). Egbe et al. have reported the benefits of post-operative anticoagulation on pulmonary bioprosthesis durability (69), suggesting an interaction between device thrombosis and premature deterioration. A failed pulmonary bioprosthesis can display an abundant pannus overgrowth (9). Pannus pathogenesis arises from multiple factors such as the tissue valve origin, the glutaraldehyde fixation, the shear stress conditions and the proximity with host tissues. In addition, some clinicopathological studies hypothesized that thrombus material could be the primary cause of pannus formation, generating, progressive valvular stenosis along with device calcification (70).

Actually, cases of thrombosis have been reported with the Edwards transcatheter valves in the pulmonary position, which were successfully treated with anticoagulant therapy (71).

In the aortic position, SAPIEN 3 leaflet thrombosis have been associated with asymmetrical or underexpanded device deployment, rather than the size of the implanted valve (72).

This is in line with the aforementioned hypothesis that valve misdeployment caused by bioprosthesis size mismatch, which is reflected in the stent diameter to invasive balloon conduit diameter ratio, may be a reliable predictive factor for valve deterioration.

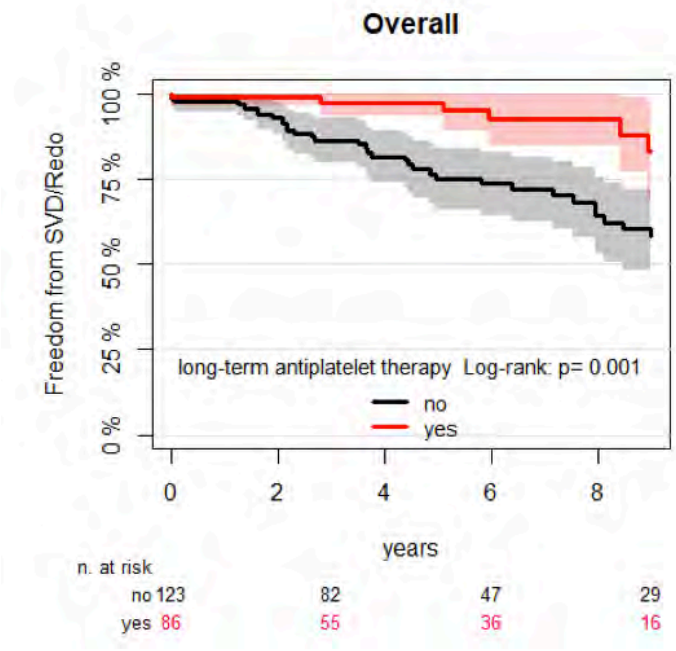


Figure 14. Freedom from structural valve deterioration (SVD)/reintervention in patients receiving homografts or bioprostheses stratified by long term (>6 months) antiplatelet therapy following surgery. Extracted from Cocomello and al., JAHA 2019

b) Infective endocarditis

McElhinney and al. noticed, in the combined study of 3 prospective North American and European Melody valve trials, that some cases of infective endocarditis occurred following the aspirin therapy discontinuation (13). This had been already reported in the preliminary publication warning of the risk of occurrence of atypical late infections (71), and was confirmed in a following prospective register (72). Further investigations performed by Jalal and al. found that the bovine jugular vein substitute of the device was possibly responsible for that increased incidence of infective disorder. Additionally, in vitro experiments provided important evidences suggesting a possible common pathway linking platelets function to bacterial adhesion and proliferation (14). This was consistent with previous researches that found a marked role of the platelets in biofilm formation and resistance to antibiotics. However, the authors described only a mild protective effect of the aspirin medication (73), in line with the lack of difference in the rate of incidence of infective endocarditis between cohorts with and without antiplatelet therapy (12). This result may arise from the recently described netosis phenomenon in the setting of infection diseases. It involves an alternative pathway of platelet and coagulation activation, which is less responsive to commonly employed therapeutics (74).

2. Stents

Even if intravascular stents still don't have specific approval for right ventricular outflow tract diseases their use has been widely accepted by professional medical societies. The conception of the ideal device applying to general congenital heart diseases may present several specific characteristics (table 4)(75).

(1) low stent profile
(2) high trackability
(3) flexibility to negotiate steep curves
(4) good radio-opacity and visibility for precise placement
(5) compatibility with magnetic resonance imaging (MRI) with no artifacts
(6) predictable expansion with minimal foreshortening
(7) sufficient radial strength
(8) low rigidity with no material fatigue over time
(9) full biocompatibility with resistance to thrombus formation and corrosion
(10) prevention of plaque protrusion
(11) avoidance of neointimal proliferation
(12) round and soft edges for avoidance of intimal damage
(13) possibility of redilation with patients' growth
(14) wide struts to maintain blood flow to jailed vessel branches
(15) retrievability and possibility of repositioning if needed.

Table 4. Specific features of the ideal device for congenital heart diseases. Extracted from Peters and al., Ann Pediatr Card 2009

Regarding pulmonary valve the first endoprosthesis was the balloon expandable Palmaz stent (Johnson & Johnson, Cordis Division, Warren, NJ), a 316 L laser cut stainless steel tube that forms seven cells per row. Given its high radial force and its oversizing properties it became a very useful tool. Nevertheless, owing to its closed cell design it suffered the drawbacks of its intense rigidity, outlining a poor flexibility, and an increased foreshortening, as well as a risk of vessel or balloon rupture due to sharp edges. Even if the NuMED Balloon In Balloon (BIB) catheter (NuMED, Inc., Nicholville, NY) solved part of the issue regarding vascular injury, enabling a secure Palmaz stent implantation in pulmonary tracts, further investigations were necessary to improve endovascular prosthesis technology.

To overcome those limitations John P. Cheatham designed the designed the NuMED Cheatham Platinum (CP) stent (NuMED, Inc, Nicholville, NY) for exclusive use in pediatric cardiology. The platinum alloys displays attractive features of higher radiopacity and better malleability. Its wire pattern made of 6, 8 or 10 « zigs » defines close cells, welded at each joint. Thus, it warrants the availability of multiple stent diameters, precluding excessive overdilation that exposes to the risk of loss of length. This welded device features particular flexibility, however the radial strength tends to be lesser than slotted tubes (such as Palmaz or IntraStent) (Figure 16).

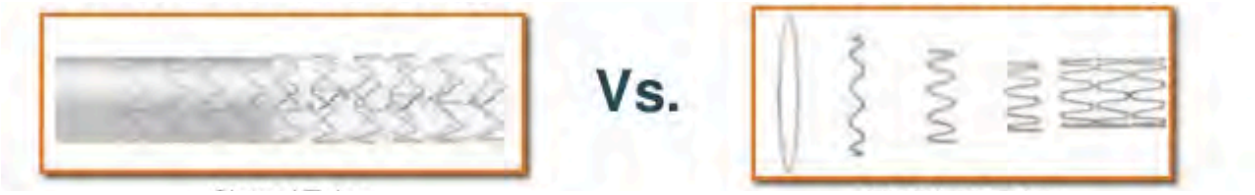


Figure 15. Comparison of slotted (left) versus welded (right) stent design. Illustration taken from Medtronic ® website

Because of its interesting profile, it was decided that it would be the framework for the Melody valve. However, following clinical trials assessing either the pulmonary valve or the endoprosthesis in aortic coarctation, revealed some safety concerns regarding the high rate of stent fractures (30). In response to that adverse event, prestenting became a routine practice. Despite those preventive measures, pre-implantation with a CP stent was still associated with a trend towards an increased risk for Melody stent fracture, compared to Palmaz stent (33). It is noteworthy to mention that the covered CP stent is particularly of interest in the treatment or prevention of most conduit injuries.

In the meantime the IntraStent™ Double Strut™ (EV3 Inc., Plymouth, MN, USA), an open-cell design stent manufactured from a laser cut stainless steel tube, became available. Its safety and efficacy in tortuous vascular obstructions, and the advantages of its unique cell geometry for the access of jailed branches, generated plenty of interest among interventional cardiologists dealing with congenital heart diseases. However, clinical reports overtime raised concerns about some weaknesses of the device. Overexpanding the stent in obstructed right outflow tracts possibly causes deformation of the open-cells, leading to vessel recoil, and protrusion of intimal tissue (31,32,76) (Figure 17).

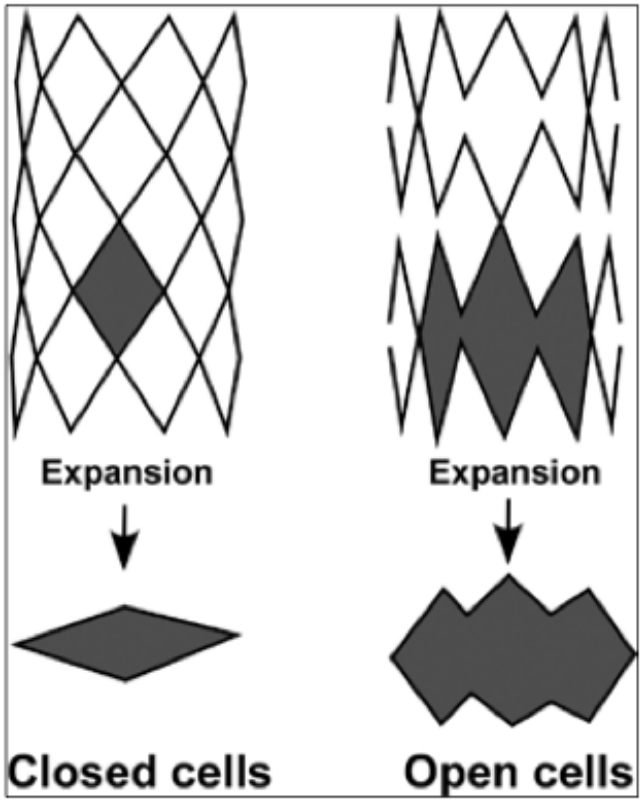


Figure 16. Cell design patterns. Extracted from Peters and al., Ann Pediatr Card 2009

In line with this overall experience, Andramed introduced a hybrid cell design stent, combining open and closed cells. The Andrastent XL and XXL (Andramed, Reutlingen, Germany) is made of cobalt chromium alloys that is known to be fracture resistant. Its use is progressively increasing even though specific data concerning pulmonary replacement are scarce (77).

Regarding pre-stenting in percutaneous valve replacement, as smaller and more obstructed right outflow tract are risk factors for stent fractures (33), it should be recommended to choose a single stent strategy to preclude decreasing conduit lumen diameter, while ensuring a reliable radial force to prevent device recoil. Considering this approach, close-cell design and stainless endoprosthesis could be preferentially implemented.

3. New valves

Ongoing trials are evaluating the non-inferiority of Edwards SAPIEN III versus XT in the pulmonic position (NCT02744677, NCT02777892, NCT03130777). The rationale of this evolution has emerged from the experience in the aortic location, that suggested a

better profile of the SAPIEN III device, designed to provide a more precise delivering system while decreasing the risk of post-procedural paravalvular leak (78). Moreover, the Edwards firm has evaluated the Alterra self-expanding prestent (NCT03130777) to allow future valve implantation in conduits currently not suitable for balloon expandable valves, because of dimensions beyond the available diameters (Figure 18).

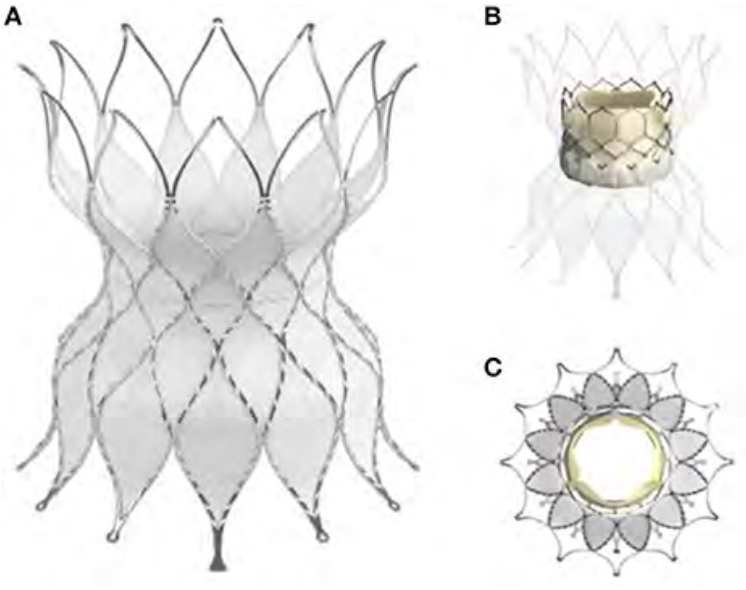


Figure 17. The Edwards Alterra adaptive pre-stent, illustration taken from Gareth J. Morgan, Front. Pediar. 2018

To overcome the size restrictions of the Melody valve, restrained to small conduits diameters, the Medtronic Company is innovating with a new self-expanding porcine pericardium valve, called Harmony™ TPV. Large regurgitant native or patch-repaired right ventricular outflow tracts are the target population, as they are currently not eligible and neither comprised among the different indications of Melody valve implantation. Therefore, the device was designed in an asymmetric manner to fit in large vessels : the outflow diameter is 34 mm, the inflow diameter is 42 mm and the outer diameter at the valved section is 23,5mm (Figure 19). Preliminary data showed that, despite a strict screening (only 32% of the participants were considered eligible), among the 20 patients implanted, 2 were explanted after 3 months follow-up, because of device migration and type II stent fracture with associated partial frame collapse, respectively. Of note, 2 additional subjects presented type I stent fracture (79). A pivotal study is recruiting 100 patients in the United States, Canada and Japan to further examine the safety and efficacy of the device (NCT02979587).

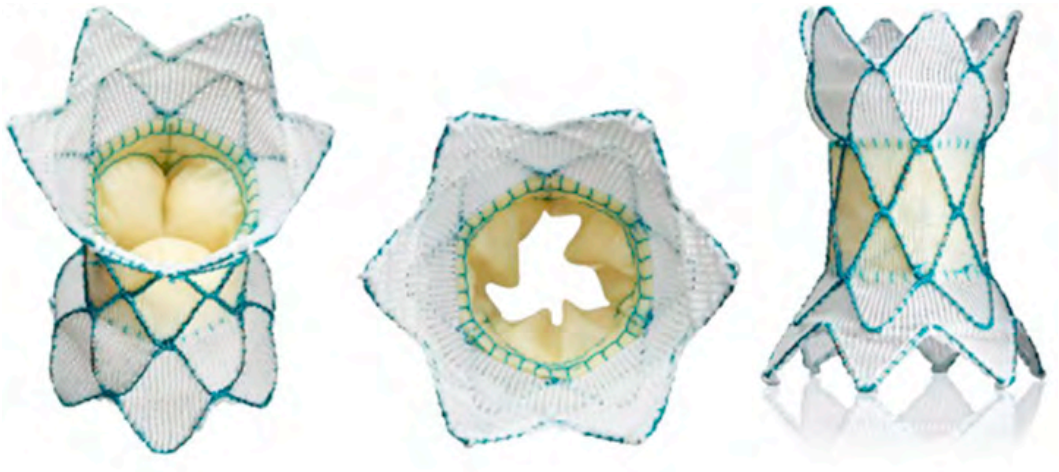


Figure 18. The Harmony transcatheter pulmonary valve (Medtronic, Minneapolis, Minnesota), illustration taken from Bergersen and al. JACC 2017

The venous P® transcatheter valve system (Venus Medtech, Shanghai, China), an other self-expanding porcine pericardium valve, is being studied. This device aspires to provide an appropriate treatment to very large native pulmonary tracts. The valve presents flared ends, uncovered only in its outflow extremity because of the proximity with pulmonary bifurcation (Figure 20). Valved-section diameter range from 20 to 30mm, in 2mm increments. Only few case series are currently available, reporting good results of the procedure (80). Ongoing larger multicenter trials (NCT02846753, NCT02590679) will provide more reliable data.

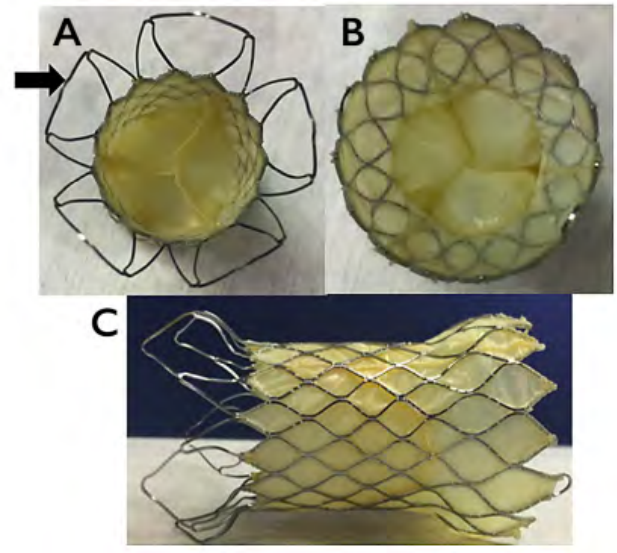


Figure 19. Venus P valve, illustration taken from Alkashkari and al., JSHD 2018

VI. Conclusion

To date, no studies have specifically reported the long-term follow-up of the Edwards SAPIEN XT valve implanted in the pulmonary position. The present multicenter prospective study confirms the valve reliability over time (up to 7.5 years), and identifies a patient profile associated with an uncertain benefit-risk balance. Excessive mismatch between the largest implanted stent and the invasive balloon conduit diameter seems to be associated with recurrent obstruction and a high rate of reintervention. Further investigations are required to confirm this preliminary finding.

In the future we could then consider, without safety concerns, treating younger patients, to prevent aggravating ventricular dysfunction, and albeit the potential risk of reintervention. Doing so involves the cardiac surgeons to avoid implanting small conduits, but rather large stented-bioprosthesis when feasible, to not preclude a future efficient percutaneous valve replacement.

Taking this a step further, we provide here the required evidences of efficiency and durability, to proceed to trials assessing the remaining critical interrogation of the optimal timing and the clinical benefits of an early percutaneous pulmonary valve replacement compared to a standard-of-care.

VII. Bibliography

1. Khoshnood B, Lelong N, Houyel L, Thieulin A-C, Jouannic J-M, Magnier S, et al. Prevalence, timing of diagnosis and mortality of newborns with congenital heart defects: a population-based study. Heart. 2012;98(22):1667-73.

2. Khairy P, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing mortality in congenital heart disease. J Am Coll Cardiol. 2010;56(14):1149-57.

3. Hoffman JIE, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39(12):1890-900.

4. Cocomello L, Meloni M, Rapetto F, Baquedano M, Ordoñez MV, Biglino G, et al. Long‐Term Comparison Between Pulmonary Homograft Versus Bioprosthesis for Pulmonary Valve Replacement in Tetralogy of Fallot. JAHA 2019

5. Batlivala SP, Emani S, Mayer JE, McElhinney DB. Pulmonary valve replacement function in adolescents: a comparison of bioprosthetic valves and homograft conduits. Ann Thorac Surg. 2012;93(6):2007-16.

6. Fiore AC, Rodefeld M, Turrentine M, Vijay P, Reynolds T, Standeven J, et al. Pulmonary Valve Replacement: A Comparison of Three Biological Valves. The Annals of Thoracic Surgery. 2008;85(5):1712-8.

7. Kwak JG, Bang JH, Cho S, Kim ER, Shih BC-H, Lee C-H, et al. Long-term durability of bioprosthetic valves in pulmonary position: Pericardial versus porcine valves. J Thorac Cardiovasc Surg. 2020;

8. Butany J, Leong SW, Cunningham KS, D'Cruz G, Carmichael K, Yau TM. A 10-year comparison of explanted Hancock-II and Carpentier-Edwards supraannular bioprostheses. Cardiovasc Pathol. 2007;16(1):4-13.

9. Soor GS, Leong SW, Butany J, Shapero JL, Williams WG. Pulmonary Site Bioprostheses: Morphologic Findings in 40 Cases. Archives of Pathology & Laboratory Medicine. 2009;133(5):797-802.

10. Khanna AD, Hill KD, Pasquali SK, Wallace AS, Masoudi FA, Jacobs ML, et al. Benchmark Outcomes for Pulmonary Valve Replacement Using The Society of Thoracic Surgeons Databases. The Annals of Thoracic Surgery. 2015;100(1):138-46.

11. Bonhoeffer P, Boudjemline Y, Saliba Z, Merckx J, Aggoun Y, Bonnet D, et al. Percutaneous replacement of pulmonary valve in a right-ventricle to pulmonary-artery prosthetic conduit with valve dysfunction. The Lancet. 2000;356(9239):1403-5.

12. Cools B, Brown S, Budts W, Heying R, Troost E, Boshoff D, et al. Up to 11 years of experience with the Melody valved stent in the right ventricular outflow tract. EuroIntervention. 2018;14(9):e988-94.

13. McElhinney DB, Benson LN, Eicken A, Kreutzer J, Padera RF, Zahn EM. Infective Endocarditis After Transcatheter Pulmonary Valve Replacement Using the Melody Valve: Combined Results of 3 Prospective North American and European Studies. Circ Cardiovasc Interv. 2013;6(3):292-300.

14. Jalal Z, Galmiche L, Lebeaux D, Villemain O, Brugada G, Patel M, et al. Selective propensity of bovine jugular vein material to bacterial adhesions: An in-vitro study. International Journal of Cardiology. 2015;198:201-5.

15. Garay F, Webb J, Hijazi ZM. Percutaneous replacement of pulmonary valve using the Edwards-Cribier percutaneous heart valve: First report in a human patient. Cathet Cardiovasc Intervent. 2006;67(5):659-62.

16. Plessis J, Hascoët S, Baruteau A, Godart F, Le Gloan L, Warin Fresse K, et al. Edwards SAPIEN Transcatheter Pulmonary Valve Implantation. JACC: Cardiovascular Interventions. 2018;11(19):1909-16.

17. Kenny D, Rhodes JF, Fleming GA, Kar S, Zahn EM, Vincent J, et al. 3-Year Outcomes of the Edwards SAPIEN Transcatheter Heart Valve for Conduit Failure in the Pulmonary Position From the COMPASSION Multicenter Clinical Trial. JACC: Cardiovascular Interventions. 2018;11(19):1920-9.

18. Caughron H, Kim D, Kamioka N, Lerakis S, Yousef A, Maini A, et al. Repeat Pulmonary Valve Replacement. JACC: Cardiovascular Interventions. 2018;11(24):2495-503.

19. Zhou Y, Xiong T, Bai P, Chu C, Dong N. Clinical outcomes of transcatheter versus surgical pulmonary valve replacement: a meta-analysis. J Thorac Dis. 2019;11(12):5343-51.

20. Ou-Yang W-B, Qureshi S, Ge J-B, Hu S-S, Li S-J, Yang K-M, et al. Multicenter Comparison of Percutaneous and Surgical Pulmonary Valve Replacement in Large RVOT. The Annals of Thoracic Surgery. 2020

21. Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, et al. 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease. Journal of the American College of Cardiology. 2019;73(12):e81-192.

22. Blackman DJ, Saraf S, MacCarthy PA, Myat A, Anderson SG, Malkin CJ, et al. Long-Term Durability of Transcatheter Aortic Valve Prostheses. J Am Coll Cardiol. 2019;73(5):537-45.

23. Baumgartner H, Bonhoeffer P, De Groot NMS, de Haan F, Deanfield JE, Galie N, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J. 2010;31(23):2915-57.

24. Silversides CK, Marelli A, Beauchesne L, Dore A, Kiess M, Salehian O, et al. Canadian Cardiovascular Society 2009 Consensus Conference on the management of adults with congenital heart disease: Executive summary. Canadian Journal of Cardiology. 2010;26(3):143-50.

25. Tretter JT, Friedberg MK, Wald RM, McElhinney DB. Defining and refining indications for transcatheter pulmonary valve replacement in patients with repaired tetralogy of Fallot: Contributions from anatomical and functional imaging. International Journal of Cardiology. 2016;221:916-25.

26. Cheatham JP, Hellenbrand WE, Zahn EM, Jones TK, Berman DP, Vincent JA, et al. Clinical and hemodynamic outcomes up to 7 years after transcatheter pulmonary

valve replacement in the US melody valve investigational device exemption trial. Circulation. 2015;131(22):1960-70.

27. Shahanavaz S, Qureshi AM, Levi DS, Boudjemline Y, Peng LF, Martin MH, et al. Transcatheter Pulmonary Valve Replacement With the Melody Valve in Small Diameter Expandable Right Ventricular Outflow Tract Conduits. JACC: Cardiovascular Interventions. 2018;11(6):554-64.

28. Nombela-Franco L, Ribeiro HB, Urena M, Pasian S, Allende R, Doyle D, et al. Incidence, predictive factors and haemodynamic consequences of acute stent recoil following transcatheter aortic valve implantation with a balloon-expandable valve. EuroIntervention. 2014;9(12):1398-406.

29. Garg A, Parashar A, Agarwal S, Aksoy O, Hammadah M, Poddar KL, et al. Comparison of acute elastic recoil between the SAPIEN-XT and SAPIEN valves in transfemoral-transcatheter aortic valve replacement: Comparison of Acute Elastic Recoil. Cathet Cardiovasc Intervent. 2015;85(3):490-6.

30. McElhinney DB, Cheatham JP, Jones TK, Lock JE, Vincent JA, Zahn EM, et al. Stent Fracture, Valve Dysfunction, and Right Ventricular Outflow Tract Reintervention After Transcatheter Pulmonary Valve Implantation: Patient-Related and Procedural Risk Factors in the US Melody Valve Trial. Circ Cardiovasc Interv. 2011;4(6):602-14.

31. Kreutzer J, Rome JJ. Open-cell design stents in congenital heart disease: A comparison of IntraStent vs. Palmaz stents. Cathet Cardiovasc Intervent. 2002;56(3):400-9.

32. Rutledge JM, Mullins CE, Nihill MR, Grifka RG, Vincent JA. Initial experience with intratherapeutics intrastent doublestrut LD stents in patients with congenital heart defects. Cathet Cardiovasc Intervent. 2002;56(4):541-8.

33. Cabalka AK, Hellenbrand WE, Eicken A, Kreutzer J, Gray RG, Bergersen L, et al. Relationships Among Conduit Type, Pre-Stenting, and Outcomes in Patients Undergoing Transcatheter Pulmonary Valve Replacement in the Prospective North

American and European Melody Valve Trials. JACC: Cardiovascular Interventions. 2017;10(17):1746-59.

34. Hadeed K, Hascoët S, Amadieu R, Dulac Y, Breinig S, Cazavet A, et al. 3D transthoracic echocardiography to assess pulmonary valve morphology and annulus size in patients with Tetralogy of Fallot. Arch Cardiovasc Dis. 2016;109(2):87-95.

35. Martin C, Sun W. Transcatheter Valve Underexpansion Limits Leaflet Durability: Implications for Valve-in-Valve Procedures. Ann Biomed Eng. 2017;45(2):394-404.

36. Carr M, Bergersen L, Marshall AC, Keane JF, Lock JE, Emani SM, et al. Bare metal stenting for obstructed small diameter homograft conduits in the right ventricular outflow tract. Cathet Cardiovasc Intervent. 2013;81(1):E44-52.

37. Silvilairat S, Cabalka AK, Cetta F, Hagler DJ, O'Leary PW. Echocardiographic assessment of isolated pulmonary valve stenosis: which outpatient Doppler gradient has the most clinical validity? J Am Soc Echocardiogr. 2005;18(11):1137-42.

38. Oechslin EN, Harrison DA, Harris L, Downar E, Webb GD, Siu SS, et al. Reoperation in adults with repair of tetralogy of fallot: Indications and outcomes. The Journal of Thoracic and Cardiovascular Surgery.1999;118(2):245-51.

39. Oosterhof T, van Straten A, Vliegen HW, Meijboom FJ, van Dijk APJ, Spijkerboer AM, et al. Preoperative Thresholds for Pulmonary Valve Replacement in Patients With Corrected Tetralogy of Fallot Using Cardiovascular Magnetic Resonance. Circulation. 2007;116(5):545-51.

40. Ferraz Cavalcanti PE, Sá MPBO, Santos CA, Esmeraldo IM, Escobar RR de, Menezes AM de, et al. Pulmonary Valve Replacement After Operative Repair of Tetralogy of Fallot. Journal of the American College of Cardiology. 2013;62(23):2227-43.

41. Therrien J, Provost Y, Merchant N, Williams W, Colman J, Webb G. Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. The American Journal of Cardiology. 2005;95(6):779-82.

42. Heng EL, Gatzoulis MA, Uebing A, Sethia B, Uemura H, Smith GC, et al. Immediate and Midterm Cardiac Remodeling After Surgical Pulmonary Valve Replacement in Adults With Repaired Tetralogy of Fallot: A Prospective Cardiovascular Magnetic Resonance and Clinical Study. Circulation. 2017;136(18):1703-13.

43. Bokma JP, Winter MM, Oosterhof T, Vliegen HW, van Dijk AP, Hazekamp MG, et al. Preoperative thresholds for mid-to-late haemodynamic and clinical outcomes after pulmonary valve replacement in tetralogy of Fallot. Eur Heart J. 2016;37(10):829-35.

44. Aboulhosn JA, Lluri G, Gurvitz MZ, Khairy P, Mongeon F-P, Kay J, et al. Left and Right Ventricular Diastolic Function in Adults With Surgically Repaired Tetralogy of Fallot: A Multi-institutional Study. Canadian Journal of Cardiology. 2013;29(7):866-72.

45. Rutz T, Ghandour F, Meierhofer C, Naumann S, Martinoff S, Lange R, et al. Evolution of right ventricular size over time after tetralogy of Fallot repair: a longitudinal cardiac magnetic resonance study. Eur Heart J Cardiovasc Imaging. 2017;18(3):364-70.

46. Hickey EJ, Veldtman G, Bradley TJ, Gengsakul A, Manlhiot C, Williams WG, et al. Late risk of outcomes for adults with repaired tetralogy of Fallot from an inception cohort spanning four decades. Eur J Cardiothorac Surg. 2009;35(1):156-64.

47. Greutmann M. Tetralogy of Fallot, pulmonary valve replacement, and right ventricular volumes: are we chasing the right target? Eur Heart J. 2016;37(10):836-9.

48. Frigiola A, Hughes M, Turner M, Taylor A, Marek J, Giardini A, et al. Physiological and Phenotypic Characteristics of Late Survivors of Tetralogy of Fallot Repair Who Are Free From Pulmonary Valve Replacement. Circulation. 2013;128(17):1861-8.

49. Geva T, Mulder B, Gauvreau K, Babu-Narayan SV, Wald RM, Hickey K, et al. Preoperative Predictors of Death and Sustained Ventricular Tachycardia After Pulmonary Valve Replacement in Patients With Repaired Tetralogy of Fallot Enrolled in the INDICATOR Cohort. Circulation. 2018;138(19):2106-15.

50. Dorobantu DM, Sharabiani MTA, Taliotis D, Parry AJ, Tulloh RMR, Bentham JR, et al. Age over 35 years is associated with increased mortality after pulmonary valve replacement in repaired tetralogy of Fallot: results from the UK National Congenital

Heart Disease Audit database. European Journal of Cardio-Thoracic Surgery. 2020;ezaa069.

51. Coats L, Khambadkone S, Derrick G, Hughes M, Jones R, Mist B, et al. Physiological consequences of percutaneous pulmonary valve implantation: the different behaviour of volume- and pressure-overloaded ventricles. Eur Heart J. 2007;28(15):1886-93.

52. Lumens J, Fan C-PS, Walmsley J, Yim D, Manlhiot C, Dragulescu A, et al. Relative Impact of Right Ventricular Electromechanical Dyssynchrony Versus Pulmonary Regurgitation on Right Ventricular Dysfunction and Exercise Intolerance in Patients After Repair of Tetralogy of Fallot. J Am Heart Assoc. 2019;8(2):e010903.

53. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. Lancet. 2000;356(9234):975-81.

54. Nollert GDA, Däbritz SH, Schmoeckel M, Vicol C, Reichart B. Risk factors for sudden death after repair of tetralogy of Fallot. The Annals of Thoracic Surgery. 2003;76(6):1901-5.

55. Nollert G, Fischlein T, Bouterwek S, Böhmer C, Klinner W, Reichart B. Long-term survival in patients with repair of tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. J Am Coll Cardiol. 1997;30(5):1374-83.

56. Quattlebaum TG, Varghese J, Neill CA, Donahoo JS. Sudden death among postoperative patients with tetralogy of Fallot: a follow-up study of 243 patients for an average of twelve years. Circulation. 1976;54(2):289-93.

57. Maury P, Sacher F, Rollin A, Mondoly P, Duparc A, Zeppenfeld K, et al. Ventricular arrhythmias and sudden death in tetralogy of Fallot. Arch Cardiovasc Dis. 2017;110(5):354-62.

58. Gatzoulis MA, Till JA, Somerville J, Redington AN. Mechanoelectrical interaction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. Circulation. 1995;92(2):231-7.

59. Valente AM, Gauvreau K, Assenza GE, Babu-Narayan SV, Schreier J, Gatzoulis MA, et al. Contemporary predictors of death and sustained ventricular tachycardia in patients with repaired tetralogy of Fallot enrolled in the INDICATOR cohort. Heart. 2014;100(3):247-53.

60. Burchill LJ, Wald RM, Harris L, Colman JM, Silversides CK. Pulmonary Valve Replacement in Adults With Repaired Tetralogy of Fallot. Seminars in Thoracic and Cardiovascular Surgery: Pediatric Cardiac Surgery Annual. 2011;14(1):92-7.

61. Aleligne Y, Eyvazian VA, Reardon L, Aboulhosn J, Moore JP, Lluri G. The effects of pulmonary valve replacement on QRS duration in repaired tetralogy of Fallot patients with pulmonary regurgitation. Journal of Electrocardiology. 2019;54:36-9.

62. Bokma JP, Geva T, Sleeper LA, Babu Narayan SV, Wald R, Hickey K, et al. A propensity score-adjusted analysis of clinical outcomes after pulmonary valve replacement in tetralogy of Fallot. Heart. 2018;104(9):738-44.

63. Hascoet S, Mauri L, Claude C, Fournier E, Lourtet J, Riou J-Y, et al. Infective Endocarditis Risk After Percutaneous Pulmonary Valve Implantation With the Melody and SAPIEN Valves. JACC: Cardiovascular Interventions. 2017;10(5):510-7.

64. Egbe A, Pislaru SV, Ali MA, Khan AR, Boler AN, Schaff HV, et al. Early Prosthetic Valve Dysfunction Due to Bioprosthetic Valve Thrombosis: The Role of Echocardiography. JACC Cardiovasc Imaging. 2018;11(7):951-8.

65. Hansson NC, Grove EL, Andersen HR, Leipsic J, Mathiassen ON, Jensen JM, et al. Transcatheter Aortic Valve Thrombosis: Incidence, Predisposing Factors, and Clinical Implications. J Am Coll Cardiol. 2016;68(19):2059-69.

66. Del Trigo M, Muñoz-Garcia AJ, Wijeysundera HC, Nombela-Franco L, Cheema AN, Gutierrez E, et al. Incidence, Timing, and Predictors of Valve Hemodynamic Deterioration After Transcatheter Aortic Valve Replacement: Multicenter Registry. J Am Coll Cardiol. 2016;67(6):644-55.

67. Dangas GD, Tijssen JGP, Wöhrle J, Søndergaard L, Gilard M, Möllmann H, et al. A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement. New England Journal of Medicine. 2020;382(2):120-9.

68. De Backer O, Dangas GD, Jilaihawi H, Leipsic JA, Terkelsen CJ, Makkar R, et al. Reduced Leaflet Motion after Transcatheter Aortic-Valve Replacement. New England Journal of Medicine. 2020;382(2):130-9.

69. Egbe AC, Connolly HM, Miranda WR, Dearani JA, Schaff HV. Outcomes of Bioprosthetic Valves in the Pulmonary Position in Adults With Congenital Heart Disease. Ann Thorac Surg. 2019;108(5):1410-5.

70. Kishan C.Agarwal, William D.Edwards, Robert H.Feldt, Gordon K.Danielson, Francisco J.Puga. Clinicopathological correlates of obstructed right-sided porcine-valved extracardiac conduits. The Journal of Thoracic and Cardiovascular Surgery 1981

71. Hascoet S, Dalla Pozza R, Bentham J et al. Early outcomes of percutaneous pulmonary valve implantation using the Edwards SAPIEN 3 transcatheter heart valve system. EuroIntervention 2019; 14:1378-1385.

72. Breitbart P, Pache G, Minners J, Hein M, Schrofel H, Neumann FJ, Ruile P. Influence of prosthesis-related factors on the occurrence of early leaflet thrombosis after transcatheter aortic valve implantation. *Eur Heart J Cardiovasc Imaging*.2020;21:1082-9.

73. Patel M, Iserin L, Bonnet D, Boudjemline Y. Atypical malignant late infective endocarditis of Melody valve. The Journal of Thoracic and Cardiovascular Surgery. 2012;143(4):e32-5.

74. Malekzadeh-Milani S, Ladouceur M, Patel M, Boughenou F-M, Iserin L, Bonnet D, et al. Incidence and predictors of Melody® valve endocarditis: a prospective study. Arch Cardiovasc Dis. 2015;108(2):97-106.

75. Jung C-J, Yeh C-Y, Shun C-T, Hsu R-B, Cheng H-W, Lin C-S, et al. Platelets Enhance Biofilm Formation and Resistance of Endocarditis-Inducing Streptococci on the Injured Heart Valve. The Journal of Infectious Diseases. 2012;205(7):1066-75.

76. Travis J. Gould , Trang T. Vu , Laura L. Swystun , Dhruva J. Dwivedi , Safiah H.C. Mai , Jeffrey I. Weitz , and Patricia C. Liaw . Neutrophil Extracellular Traps Promote Thrombin Generation Through Platelet-Dependent and Platelet-Independent Mechanisms. Arteriosclerosis, Thrombosis, and Vascular Biology. 2014;34:1977–1984

77. Peters B, Ewert P, Berger F. The role of stents in the treatment of congenital heart disease: Current status and future perspectives. Ann Pediatr Cardiol. 2009;2(1):3-23.

78. Cheatham JP. Improved stents for pediatric applications. Progress in Pediatric Cardiology. 2001;14(1):95-115.

79. Venczelova Z, Tittel P, Masura J. First experience with AndraStent XL implantation in children and adolescents with congenital heart diseases. Catheter Cardiovasc Interv. 2013;81(1):103-10.

80. Arai T, Lefèvre T, Hovasse T, Morice M-C, Garot P, Benamer H, et al. Comparison of Edwards SAPIEN 3 versus SAPIEN XT in transfemoral transcatheter aortic valve implantation: Difference of valve selection in the real world. Journal of Cardiology. 2017;69(3):565-9.

81. Bergersen L, Benson LN, Gillespie MJ, Cheatham SL, Crean AM, Hor KN, et al. Harmony Feasibility Trial: Acute and Short-Term Outcomes With a Self-Expanding Transcatheter Pulmonary Valve. JACC Cardiovasc Interv. 2017;10(17):1763-73.

82. Cao Q-L, Kenny D, Zhou D, Pan W, Guan L, Ge J, et al. Early clinical experience with a novel self-expanding percutaneous stent-valve in the native right ventricular outflow tract. Catheter Cardiovasc Interv. 2014;84(7):1131-7.

NOM : LE RUZ PRENOM : Robin

Titre de Thèse : Suivi à long-terme après revalvulation pulmonaire par valve Edwards SAPIEN XT

RESUME

-**INTRODUCTION** : Bien qu'initialement conçues pour traiter le rétrécissement aortique serré, des données récentes de la littérature ont montré la sûreté et l'efficacité à court-terme des valves Edwards SAPIEN (Edwards Lifesciences, Irvine, CA, USA) implantées en position pulmonaire chez des patients présentant une pathologie de la voie d'éjection droite. Toutefois, à ce jour, aucune donnée de long-terme n'a été rapportée.
-**OBJECTIF** : L'objectif principal de cette étude est de décrire le devenir à long-terme des patients implantés d'une valve Edwards SAPIEN en position pulmonaire.
-**MATERIEL AND METHODES** : Entre 2011 et 2016, 3 centres français ont inclus consécutivement et prospectivement les patients implantés avec succés d'une valve Edwards SAPIEN XT en position pulmonaire.
-**RESULTATS**

Population :

- 62 patients furent inclus, ils présentaient une pathologie sténosante et/ou fuyante de la valve pulmonaire, soit symptomatique, soit asymptomatique mais remplissant les critères de remplacement valvulaire.

Critère de jugement principal:

- Le critère de jugement principal composite, définit par la mortalité ou la transplantation, l'endocardite infectieuse et les réinterventions au dernier suivi, était de 24,2% pour un suivi médian de 55 ± 21 mois.

Critères de jugement secondaires:

- L'incidence de la mortalité ou transplantation à 3 et 5 ans était respectivement de 8.4% (95% confidence interval (CI) 3.6-19%) et 10.6% (95% CI 4.9-22.1%).
- A 5 ans le taux d'endocardite était de 1,6% (95% CI 0.2-10.9%) correspondant à un taux de 0.35% par patient-année (95% CI 0.01-2.00%).
- L'incidence des réinterventions à 3 et 5 ans était respectivement de 3.4% (95% CI 0.9-12.9%) et 11% (95% CI 4.6-25.2%). Les réinterventions étaient exclusivement dues à une resténose sur la voie d'éjection droite.

-**CONCLUSION** : Cette étude confirme l'efficacité et la sécurité à long-terme des valves Edwards SAPIEN XT implantées en position pulmonaire, chez les patients connus pour une cardiopathie congénitale réparée et porteurs d'une pathologie de la voie d'éjection droite.

MOTS-CLES

Cardiopathies congénitales, Remplacement valvulaire percutané, Valve pulmonaire, Cardiologie structurelle

NOM : LE RUZ PRENOM : Robin

Titre de Thèse : Edwards SAPIEN XT Transcatheter Pulmonary Valve Implantation: Long-term outcomes in a French Registry

---

RESUME

Objectives: The aim of the study was to investigate patient long-term outcomes after implantation of an Edwards SAPIEN transcatheter heart valve (Edwards Lifesciences, Irvine, CA, USA) in the pulmonary position.
Background: The Edwards SAPIEN valve, which was initially designed for percutaneous aortic valve replacement has recently been successfully implanted in patients with dysfunctional right ventricular outflow tracts, but long-term follow-up has not been reported.
Methods: From 2011 to 2016, 62 patients undergoing successful transcatheter pulmonary valve replacement with an Edwards SAPIEN XT valve were consecutively included into the study. The primary composite outcome was defined as the rate of all-cause mortality or transplant, infective endocarditis, and reintervention at last follow-up. Subgroup analyses and Cox model were used to characterize the patients requiring reintervention.
Results: The primary outcome was met for 24.2% patients after a mean follow-up of 55 ± 21 months. One case of infective endocarditis was reported, whereas no significant valvular insufficiency was observed. Reinterventions were exclusively due to recurrent obstruction, Kaplan-Meier estimates at 3 and 5 years were 3.4% (95% confidence interval (CI): 0.9-12.9%) and 11% (95% CI: 4.6-25.2%), respectively. Patients requiring reintervention were younger (risk ratio: 11.8; p = 0.039). They were more likely to have a small tube-graft, a higher pulmonary gradient after the procedure and a ratio of largest implanted stent diameter to invasive balloon conduit diameter over 1.35 (p = 0.04).
Conclusions: This study confirms the long-term safety and efficacy of the Edwards SAPIEN XT valve in patients with dysfunctional right ventricular outflow tracts.

MOTS-CLES

Congenital Heart Disease, Percutaneous Valve Therapy, Structural Heart Disease Intervention, Transcatheter Valve Implantation, Pulmonary Valve Disease