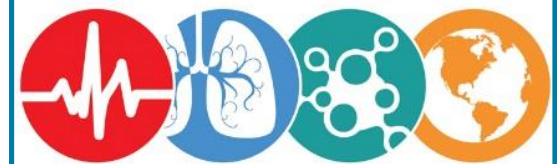


PULMONARY VALVE: INTERVENTIONAL TREATMENT

Fraisse

Royal Brompton and Harefield Hospital

London, U.K.

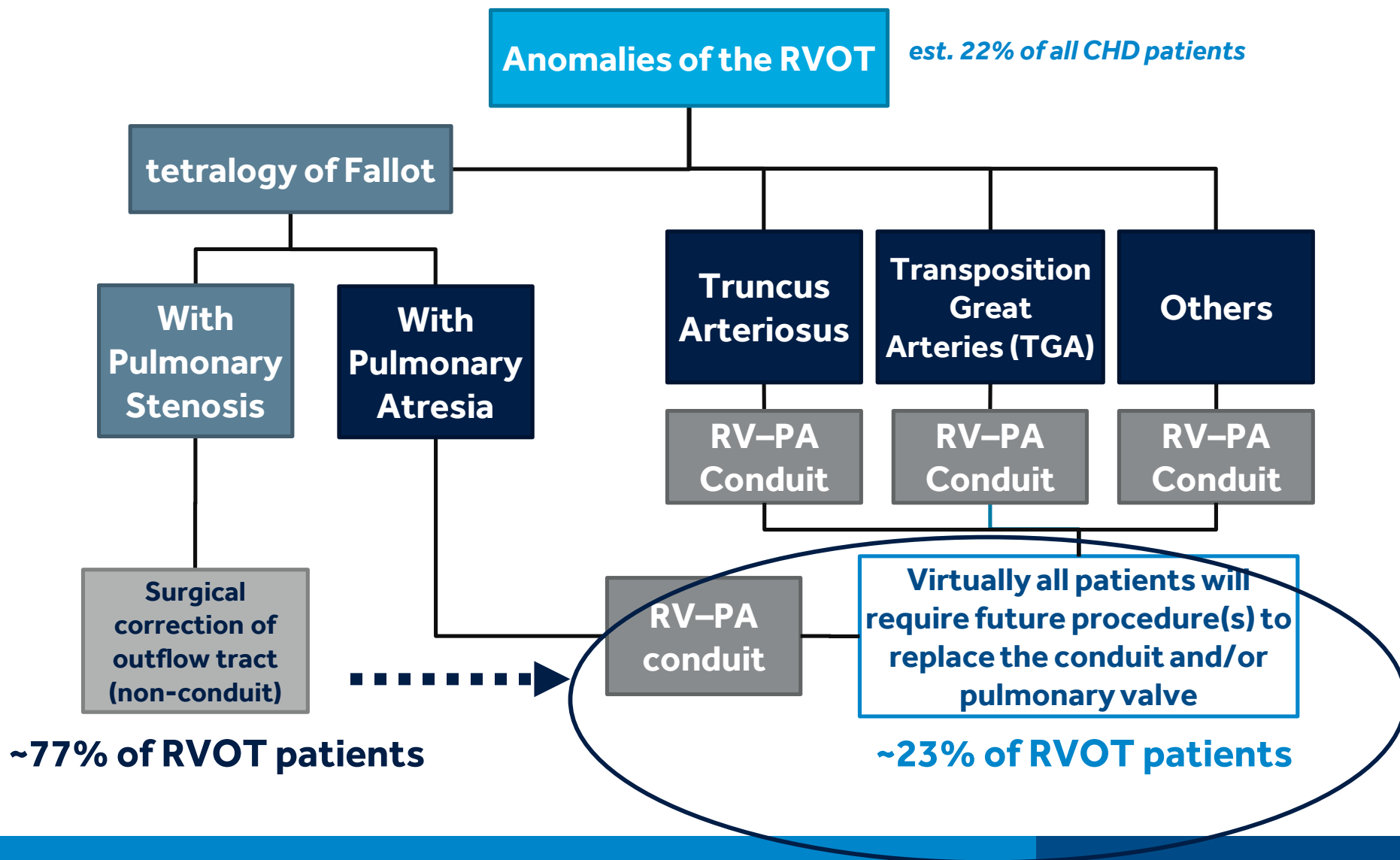


A lifetime of specialist care

CONSULTANT AND PROCTOR FOR MEDTRONIC

CONGENITAL HEART DISEASE MARKET

PATIENTS WITH RVOT ANOMALIES



MANAGEMENT OPTIONS FOR CONDUIT DYSFUNCTION

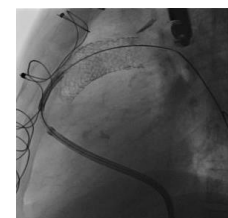
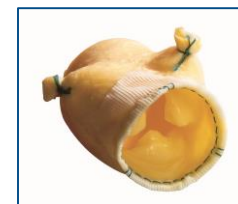
- Surgical conduit replacement

- Bioprostheses
- Homografts
- Xenografts



- Transcatheter

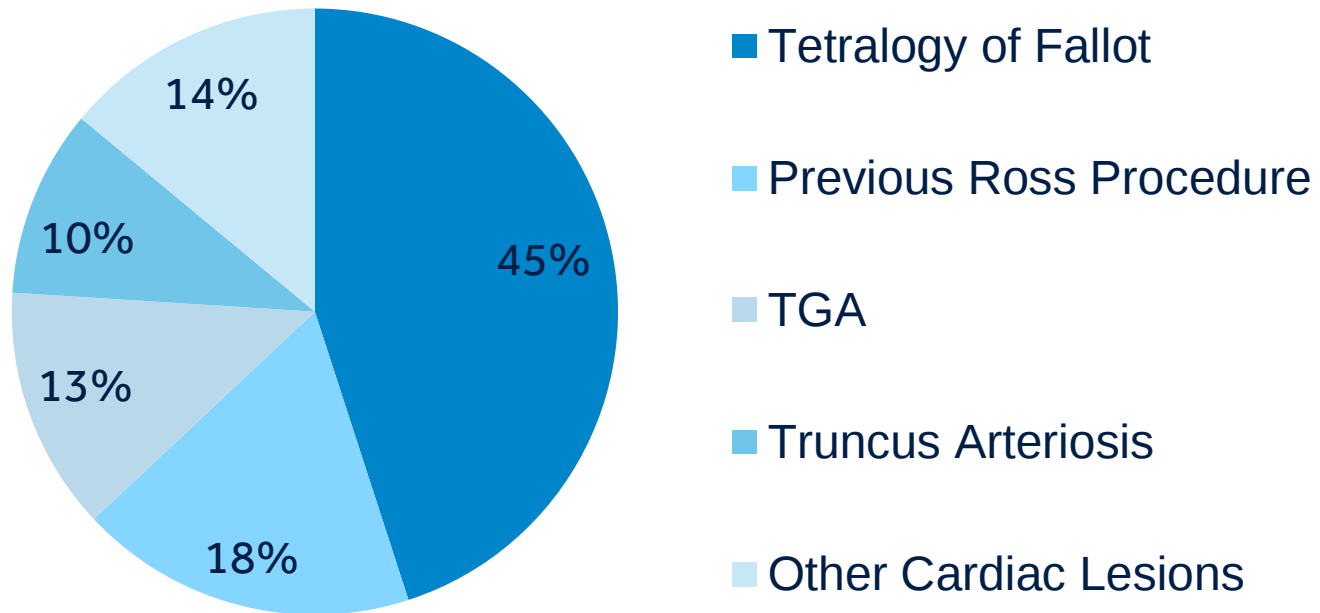
- Balloon angioplasty
- Bare metal stent
- Transcatheter Pulmonary Valve (TPV)



PATIENT CHARACTERISTICS

TRANSCATHETER PULMONARY VALVE THERAPY

Original Diagnosis*



*Combined baseline patient characteristic data from 373 patients enrolled in Melody TPV US IDE Study (171 enrolled patients), US Melody TPV Post Approval Study (151 enrolled patients), and European / Canadian Post Market Surveillance Study (71 enrolled patients). Medtronic data on file.

Edwards SAPIEN™ Transcatheter Heart Valve

Balloon-expandable, radiopaque, stainless steel frame, three bovine pericardial tissue leaflets, and a polyethylene terephthalate (PET) fabric. The bioprosthesis is treated according to the Carpentier-Edwards ThermoFix process, packaged, and terminally sterilized in glutaraldehyde.

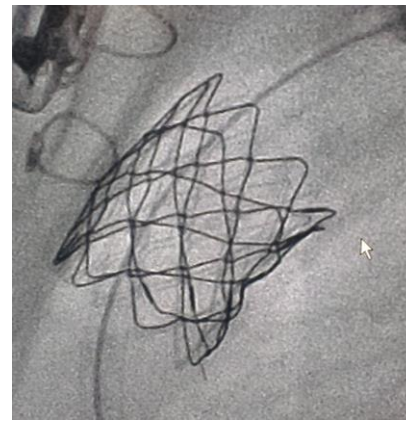
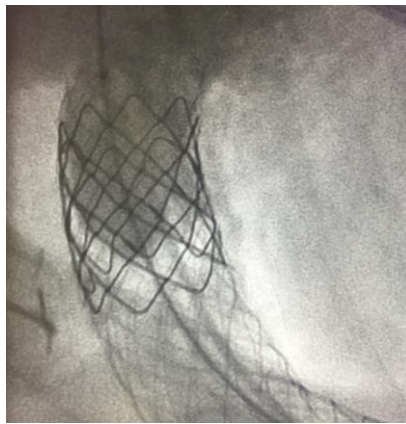
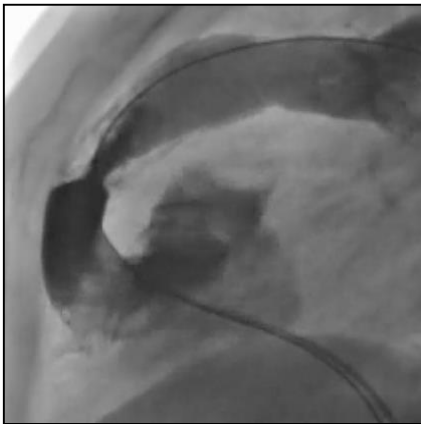
3 sizes are available 23mm, 26 and 29mm.



MELODY™ TPV THERAPY

Intended to address deleterious effects of both pressure and volume overload from RVOT conduit dysfunction (regurgitant, stenotic or combination) **without open heart surgery**

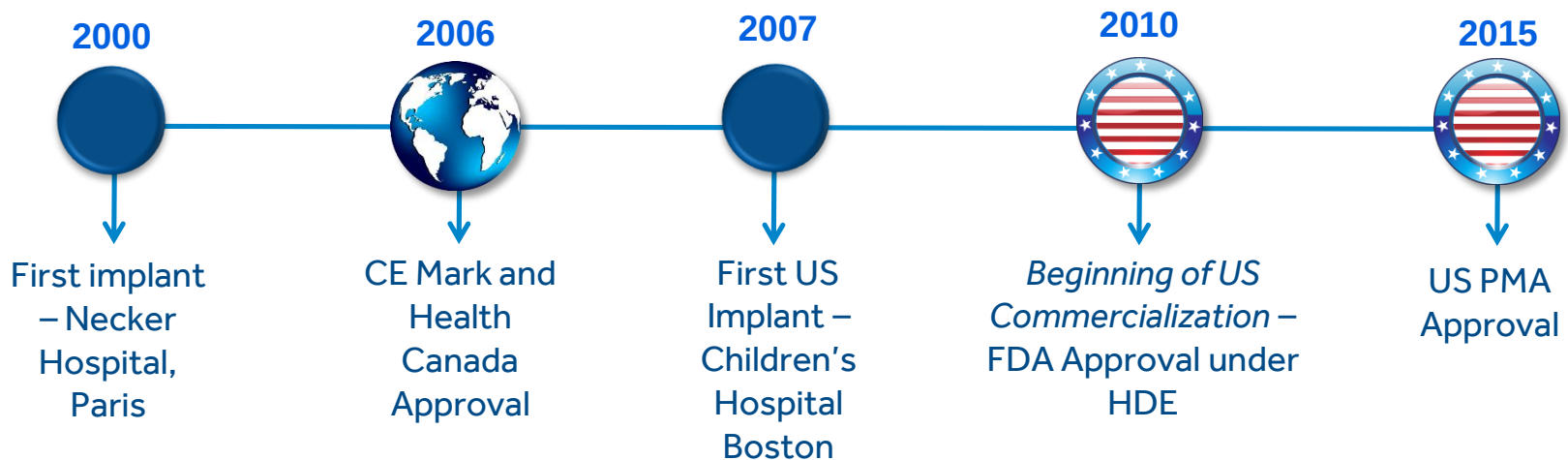
- Relieve conduit stenosis without inducing regurgitation
- Restore and maintain pulmonary valve competence *with the goal of extending RV to PA conduit life*



MELODY™ TPV SYSTEM

GLOBAL TIMELINE

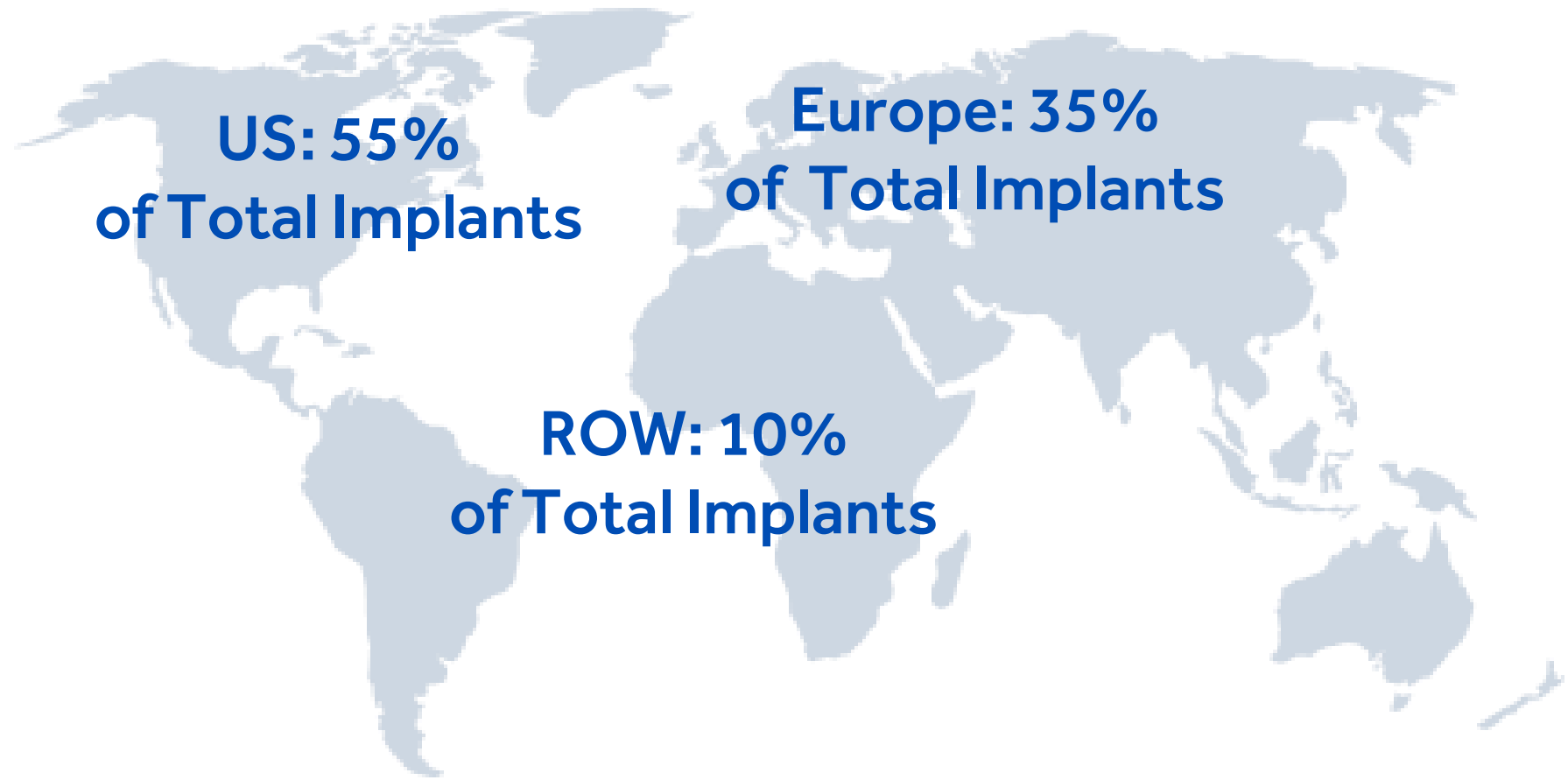
- >10,000 implants globally to date
- 300 implanting centers – 35 countries



- Significant body of clinical evidence with >400 patients under clinical study in EU and US trials
- Published follow-up data to 7 years

GLOBAL EXPERIENCE WITH MELODY™ TPV

>10,500 PATIENTS SERVED~300 CENTERS~35 COUNTRIES



*Patients through Sept 2016

MELODY™ TPV

PATIENT SELECTION CRITERIA

Patient Selection Criteria

- Objective evidence of conduit dysfunction
 - Moderate or severe regurgitation (by echo and/or MRI)
 - Right ventricular outflow obstruction
- Ability to accommodate the 22Fr delivery catheter
- Conduit originally $\geq 16\text{mm}$
- Favorable RV-PA conduit morphology
 - Amenable to valve anchorage
 - Sizing balloon (waist) diameter $\geq 14\text{mm}$ and $\leq 20\text{mm}$

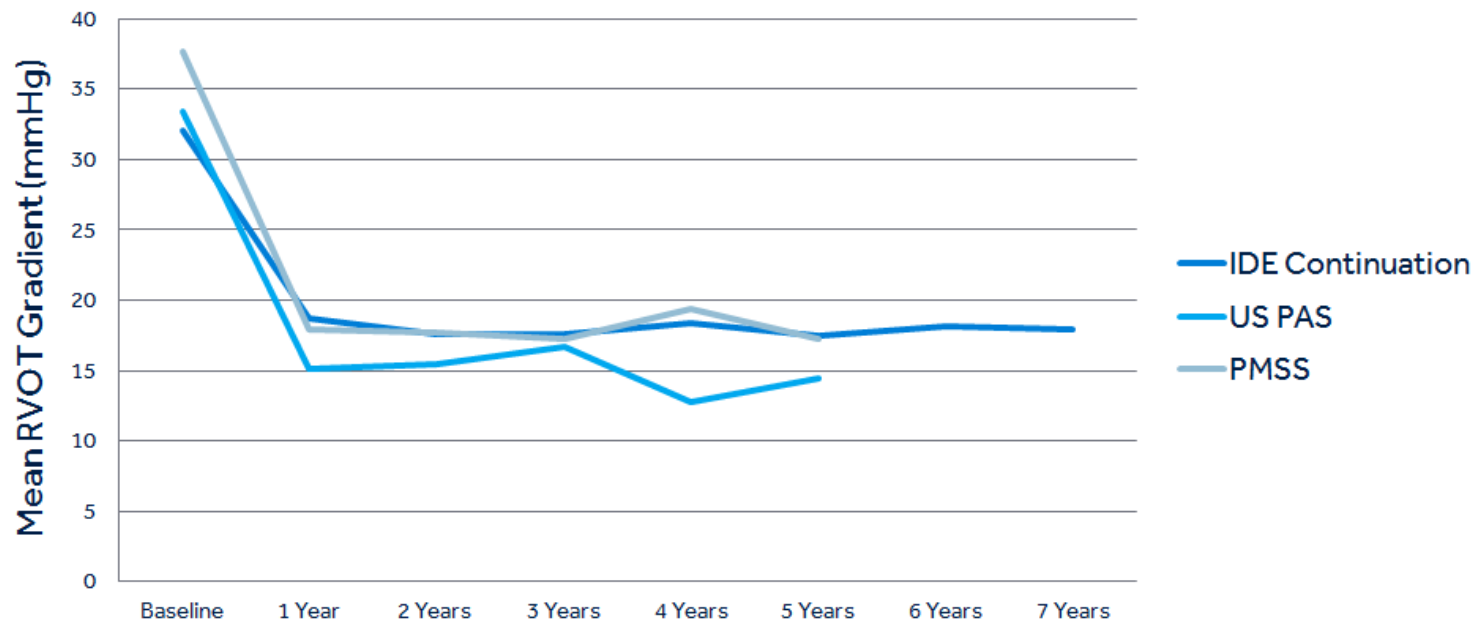
Exclusion Criteria

- Active endocarditis
- Unsuitable anatomy
- Risk of coronary occlusion

LOW RVOT GRADIENTS

Following Melody TPV implant the mean RVOT gradients decreased and remained consistent throughout follow-up

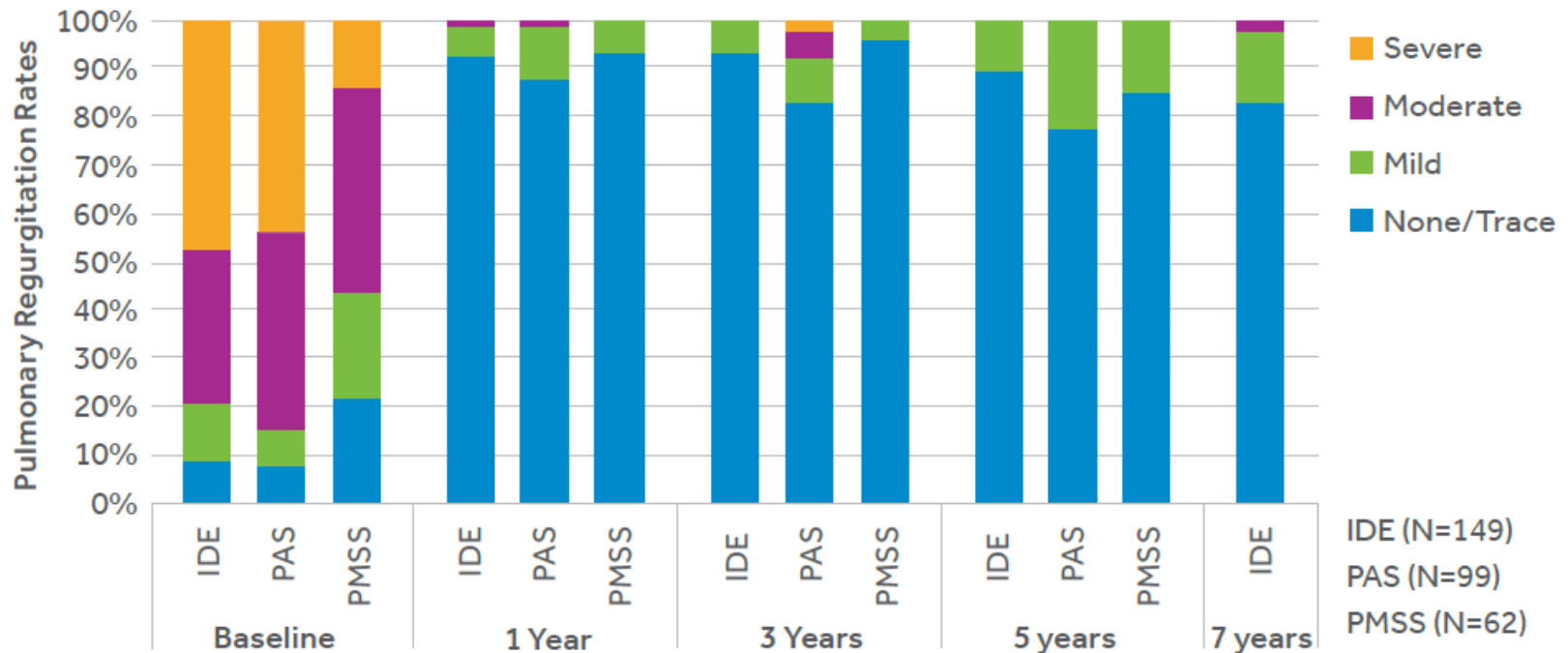
Mean RVOT Gradient By Time Interval	Baseline	1 Year	3 Year	5 Year	7 Year
US IDE (N=149)	32.1 ± 13.9	18.7 ± 9.1	17.6 ± 7.9	17.5 ± 8.4	17.9 ± 9.8
US PAS (N=99)	33.4 ± 14.1	15.1 ± 7.1	16.7 ± 10.8	14.4 ± 12.6	--
EU/CA PMSS (N=62)	37.7 ± 12.1	17.9 ± 9.2	17.3 ± 8.4	17.3 ± 9.7	--



Includes data from subjects who have undergone implantation of a subsequent Melody TPV as applicable

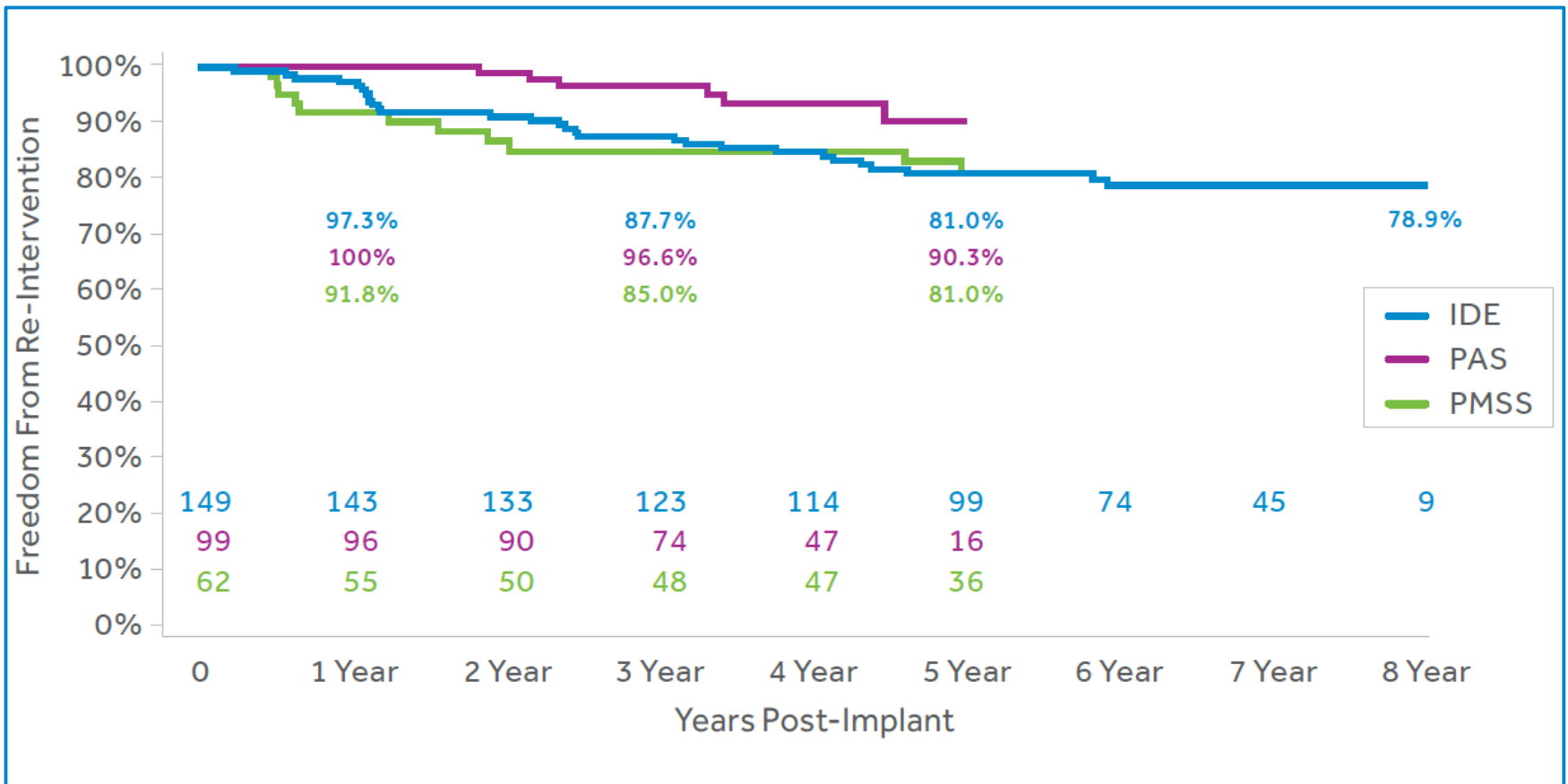
PULMONARY REGURGITATION

At baseline, the majority of subjects had moderate or severe pulmonary regurgitation. Throughout follow-up, the majority of subjects had no more than trace regurgitation.



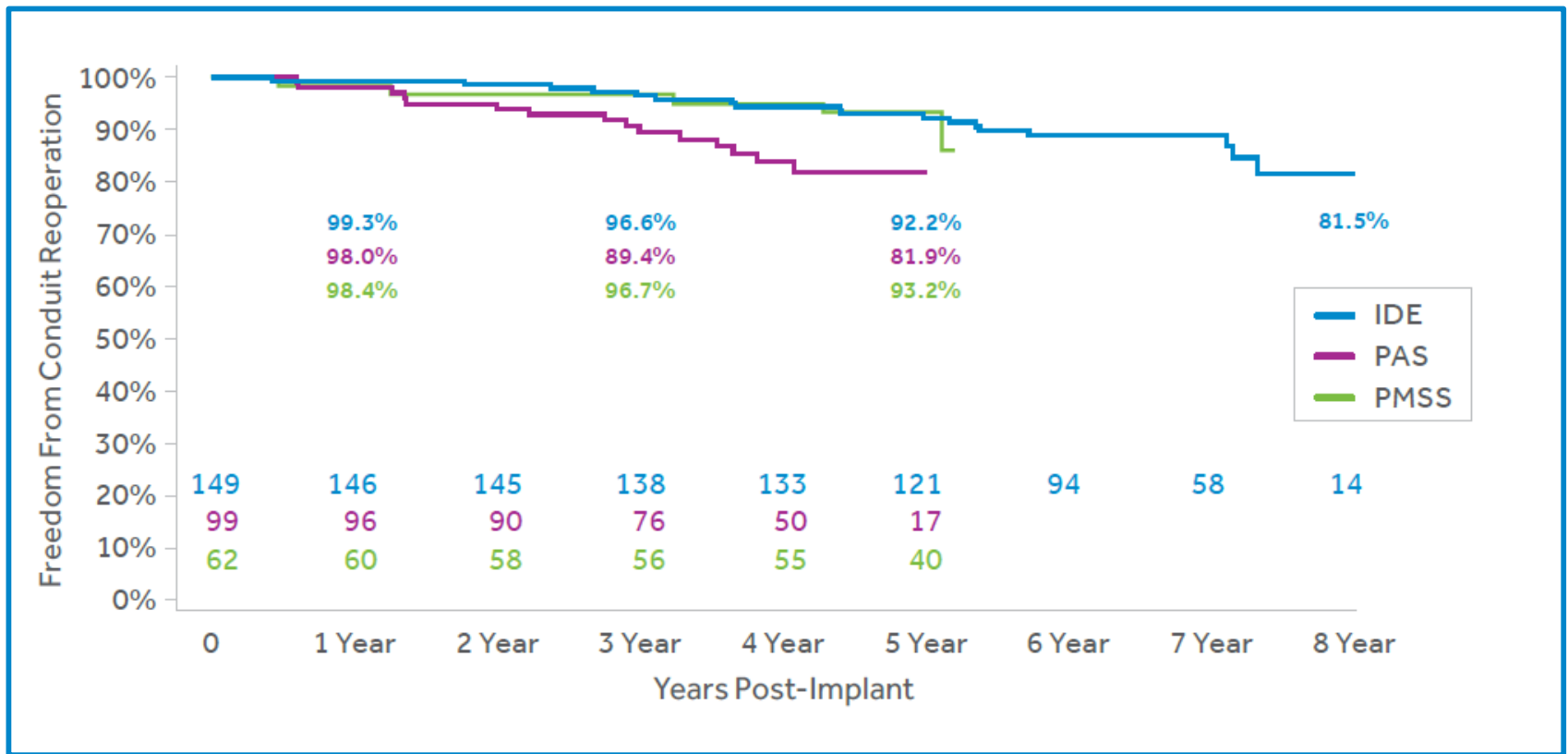
FREEDOM FROM CATHETER RE-INTERVENTION

Freedom from catheter-based re-intervention on
Melody TPV ~80% out to 7 years



FREEDOM FROM SURGICAL RE-OPERATION

Melody TPV has been proven to successfully delay surgical re-operation in the majority of patients 5 years and beyond



ENDOCARDITIS

CLINICAL DATA FROM MDT & EDW SPONSORED STUDIES

- Similar Freedom from IE rates for Melody TPV and SAPIEN based on Kaplan-Meier Analysis
 - Direct comparison of rates has limitations as EDW definition of IE unknown
- Kaplan-Meier Freedom From Valve Endocarditis***

	Number at Risk	Melody TPV
1 year	143	97.9%
2 years	141	97.3%
3 years	135	97.3%
4 years	130	97.3%
5 years	118	95.7%
6 years	91	92.1%
7 years	55	89.2%

Source: Medtronic Data on File, IDE Continuation Study

	Number at Risk	SAPIEN Pulmonic Implant
1 year	56	97.0%
2 years	44	97.0%
3 years	40	97.0%
4 years	22	93.3%
5 years	9	87.1%

Source: Edwards SAPIEN U.S. IFU 2016, COMPASSION Trial

*NOTE: The charts are not intended to be a comparison of the two devices as there is no head-to-head clinical study, but rather are intended to illustrate the clinical results of two similar trials. Multiple factors contribute to clinical study outcomes and need to be considered in making any assessments across different studies.

ONGOING RESEARCH : TRANSCATHETER PULMONARY VALVE IMPLANTATION IN SMALL RV-PA CONDUITS

S HASCOET, JD FERREIRA MARTINS, H BAHO, S KADIROVA, F PINTO, F PAOLI, F BITAR, A ABU HAWELEH, A UEBING, P ACAR, O GHEZ, A FRAISSE

Current guidelines (www.medtronic.com/safety-info-html):

- Minimal conduit size: 16 mm
- No overdilation : do not use a balloon with a diameter greater than 110% of the nominal diameter (original implant size) of the conduit for pre-dilation of the intended site of deployment, or for deployment of the TPV

Limited experience for implantation in small conduits (Berman. Circ Cardiovasc Interv. 2014)

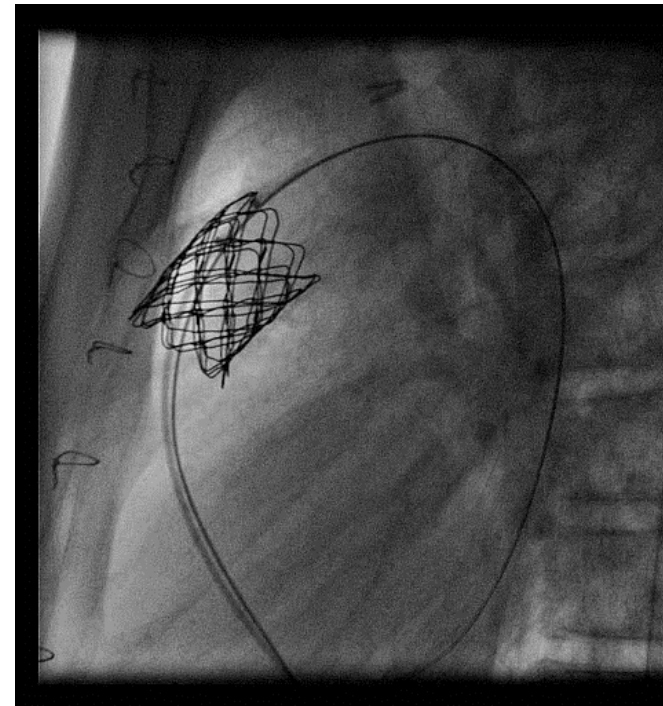
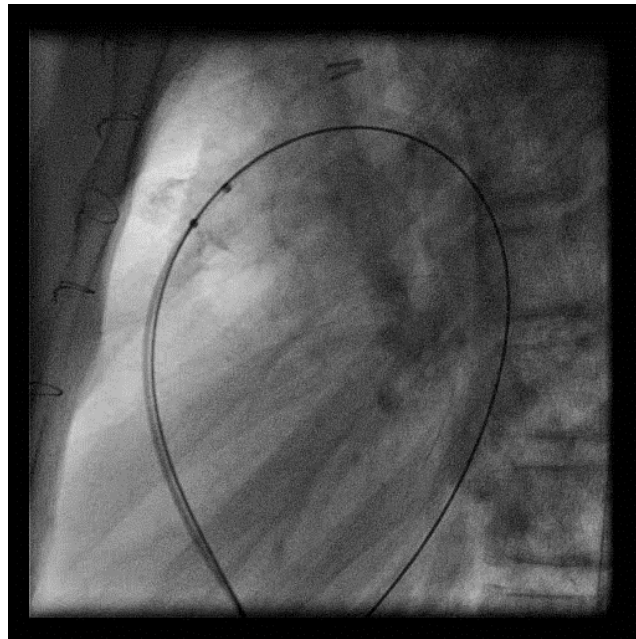
- in 4 patients, the original conduit diameter was reported to be 15 (n=3) or 12 mm (n=1; augmented surgically at previous reoperation).

Predictors and outcomes of right ventricular outflow tract conduit rupture during percutaneous pulmonary valve implantation: a multicentre study Boudjemline, Y, Malekzadeh-Milani, S; Patel, M; Thambo, JB; Bonnet, D; Iserin, L; Fraisse A. EuroIntervention 2016

- Conduit rupture occurred in nine out of 99 patients (9.09%).
- Significant risk factors included heavy calcification ($p < 0.05$, OR=16 [1.87-357]), and conduit type (homograft/others; $p < 0.05$, OR=4.37 [1.1-17.8]).
- All patients were managed in the cardiac catheterisation laboratory.
- NuMed covered stent platinum for the treatment or prevention of RVOT conduit disruption during transcatheter pulmonary valve replacement (Bishnoi et al Cath CI 2015)
- Of the 43 patients with conduit disruption only 4 had uncontained ruptures (chest tube placement in 2)

METHODS

- Retrospective study (2008-16)
- 14 patients from 8 centres
- On call surgeon present and Op theatre available
- Progressive BD of the conduit
- If conduit rupture: Long sheath with crimped covered stent ready



Patient demographics				
		(n=14)		
Age (years) mean (SD) min. max.		12.1 (3.0) 7.7 - 16		
Weigth (kg) mean (SD) min. max.		44.9 (18.3) 19 - 83		
Congenital Heart Diseases (%)				
Commun Arterial Trunk		5 (35.7%)		
Tetralogy of Fallot with Pulmonary Atresia		3 (21.4%)		
Tetralogy of Fallot with Pulmonary Stenosis		1 (7.1%)	Conduit diameter at surgical implantation	
Pulmonary valve agenesis		1 (7.1%)	12 mm	1 (7.1%)
Ross procedure		2 (14.3%)	13 mm	1 (7.1%)
Transposition of the Great Arteries		1 (7.1%)	14 mm	4 (28.6%)
Pulmonary Valve Stenosis		1 (7.1%)	15 mm	3 (21.4%)
			16 mm	2 (14.3%)
Number of surgery (%)			17 mm	2 (14.3%)
1	10 (71.4%)		18 mm	1 (7.1%)
2	4 (28.6%)	Conduit diameter at Melody valve implantation		
Right Ventricle Outflow Tract (%)			10 mm	2 (14.3%)
Homograft		10 (71.4%)	11 mm	4 (28.6%)
Valved conduit (Contegra)		3 (21.4%)	12 mm	2 (14.3%)
Non valved conduit		1 (7.1%)	13 mm	2 (14.3%)
			14 mm	3 (21.4%)
			16 mm	1 (7.1%)
			abbreviations: SD : Stand	

Conduit diameter < 16 mm

Patient	Age/weight at implantation	CHD	N° previous surgeries	Initial conduit size	Conduit diameter at implantation	Conduit	Diameter presenting/melody valve	Complications
1	15/50	PA/VSD	1	14	14	N/A	20/22	Conduit rupture
2	16/41	Fallot /absent PV	1	15	13,5	Homograft	16/18	
3	9/24,3	Truncus	1	12	11	Homograft	20/22	Conduit rupture
4	11/30	PA/VSD	1	14	12	Contegra	22/22	
5	11/42	Truncus	2	15	11	Homograft	20/20	
6	8/19	Truncus	1	14	13	Contegra	22/22	Bifurcation stent embolisation
7	7,7/28	Truncus	2	14	14	Homograft	18/18	
8	10,7/38	TOF	1	15	14	Homograft	20/22	Conduit rupture; Ao-RV communication
9	13/35	Truncus	1	13	10	Homograft	20/22	



Conduit diameter ≥ 16 mm

Patient	Age/weight at implantation	CHD	N° previous surgeries	Initial conduit size	Conduit diameter at implantation	Conduit	Diameter presenting/melody valve	Complications
1	16/83	PS	1	17	12	Homograft	22/22	Conduit rupture
2	16/71.5	AS/ Ross	1	18	16,5	Homograft	22/22	Conduit rupture
3	13/60	Critical AS	2	17	11	Homograft	22/22	Conduit rupture
5	9/50,4	PA/VSD	2	16	10	Homograft	20/22	Conduit rupture
10	14/56	TGA	1	16	11	Contegra	22/22	

OUTCOMES AND KEY LEARNINGS FOR SMALL CONDUITS IMPLANTATION

- The risk for haemothorax needing emergency surgery after conduit rupture is small due to surrounding fibrous tissue. Significant risk factors are heavy calcifications and homograft. Overexpansion of conduit is not a significant risk factor *. Very elevated RVOT conduit systolic pressure gradient is also a risk factor for conduit tear**.
- Conduit rupture is not more dangerous if this occurs in a small conduit but is clearly more frequent (50% vs 6-9%). Surgical back-up should be immediately available
- Whatever the initial size of the conduit is, one should always try to implant the largest possible valve
- Careful balloon inflation after conduit rupture is possible and might be justified to better assess coronary compressions. However, covered stent should be immediately available
- The concept to go directly from conduit implantation in neonatal period or infancy to transcatheter pulmonary valve implantation is a reality.
- *Boudjemline et al. Eurointervention 2014
- **Bishnoi et al Cath CI 2015

TRANSCATHETER PULMONARY VALVE FOR THE NATIVE OUTFLOW TRACT

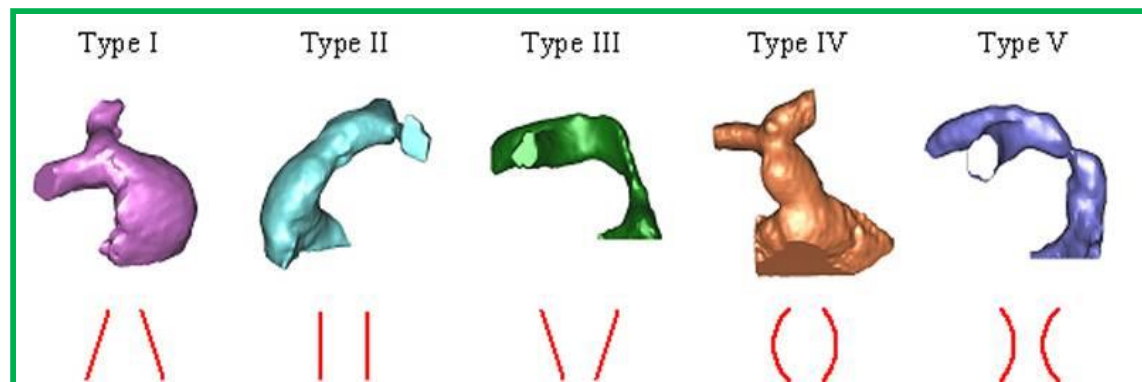
Gold Standard: surgical repair of the Pulmonary Valve
with placement of a bioprosthetic valve or conduit

Therapy Goals

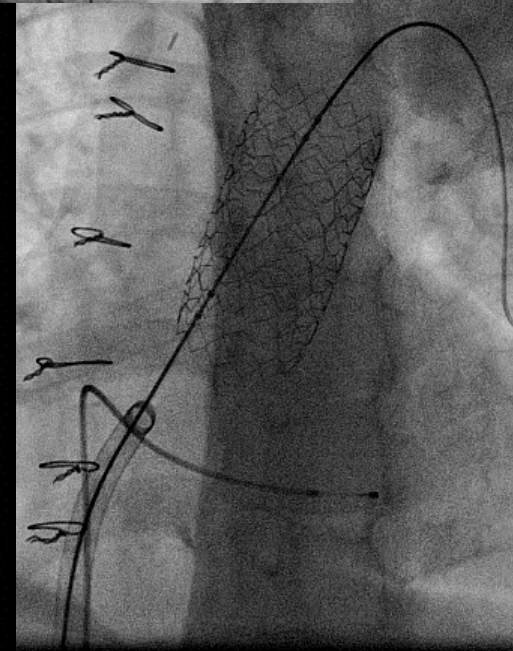
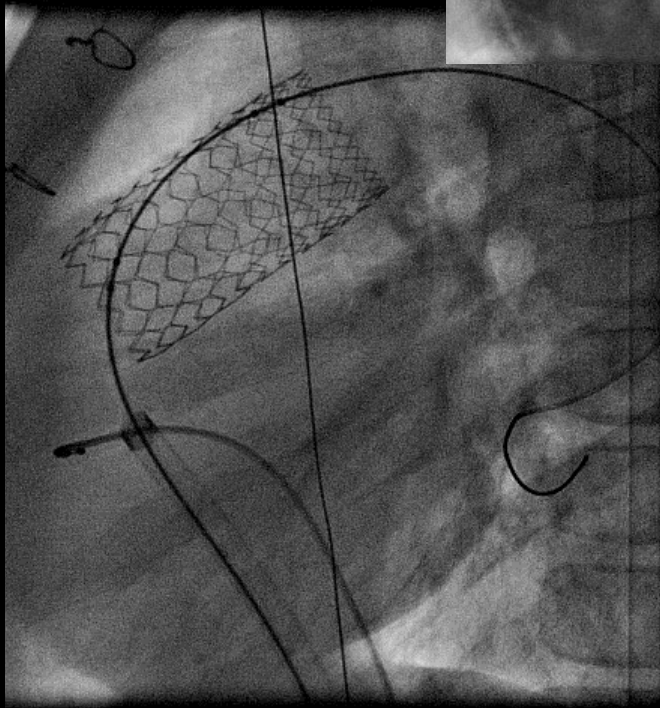
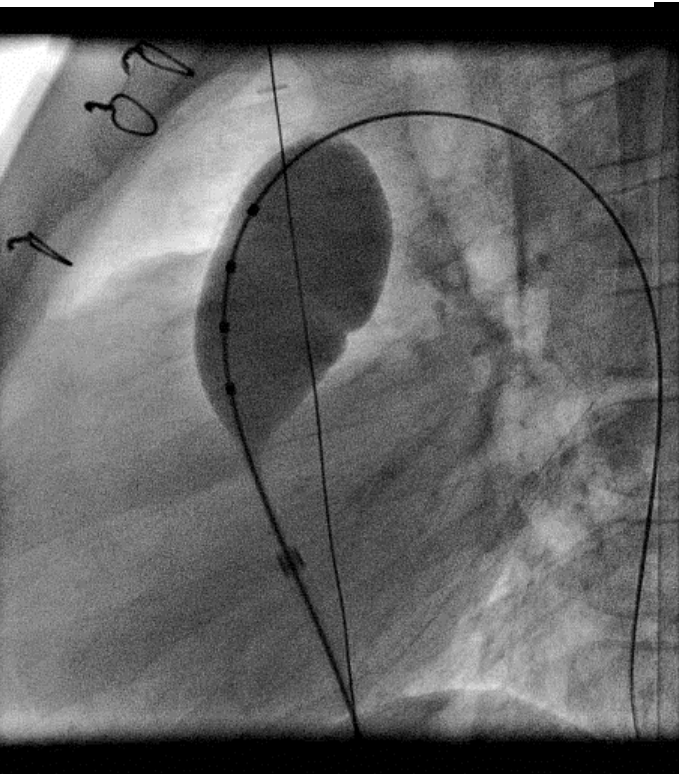
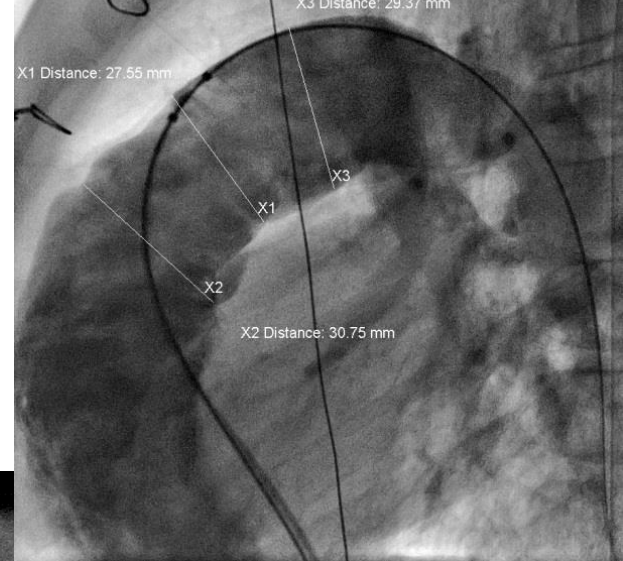
- Provide more options for tetralogy of Fallot patients over their lifetime
- Earlier intervention to address Pulmonary Insufficiency before damage to the RV becomes detrimental
- Significantly reduce invasiveness of procedure

The Challenge:

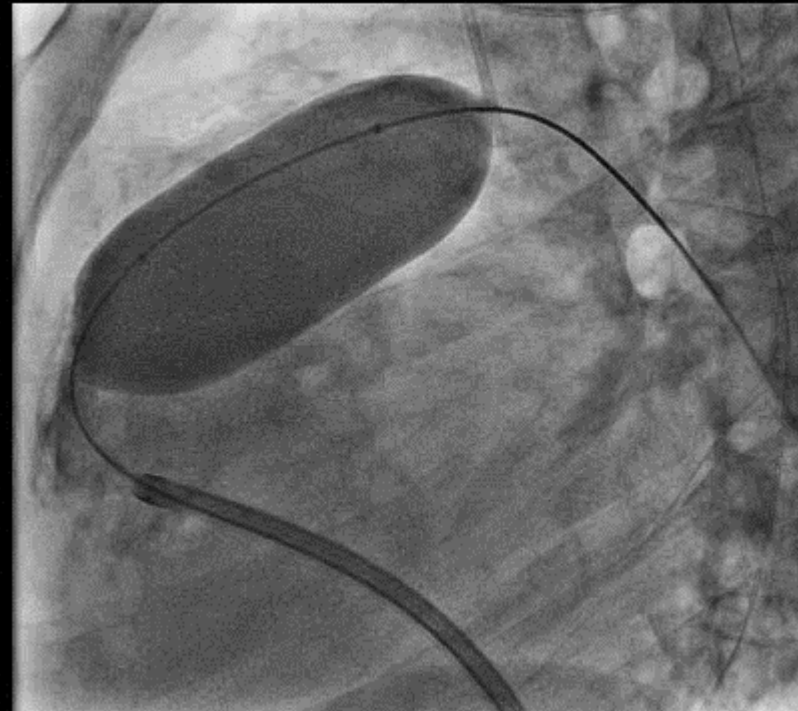
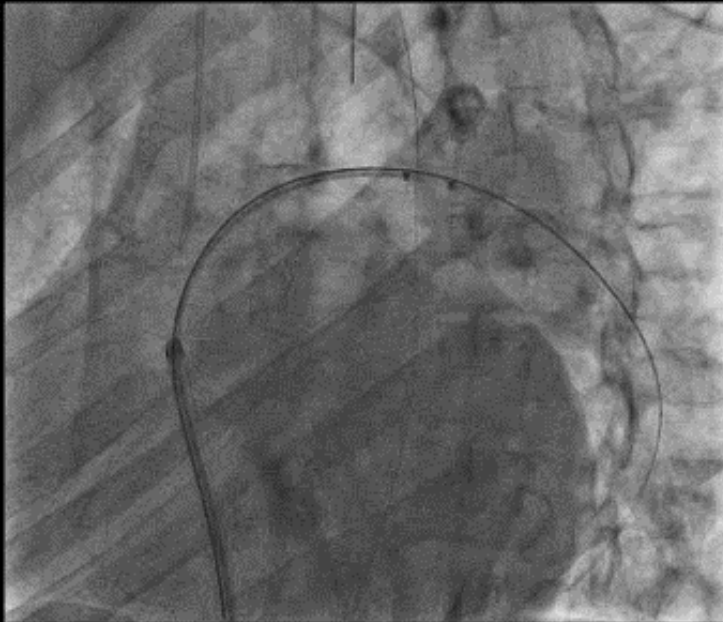
*A device that is versatile
enough to address wide
variability in patient anatomies*

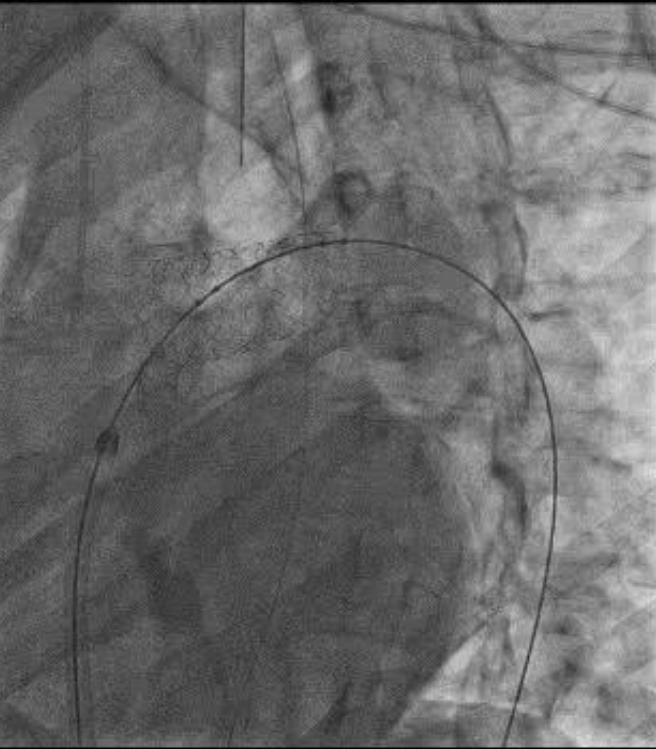


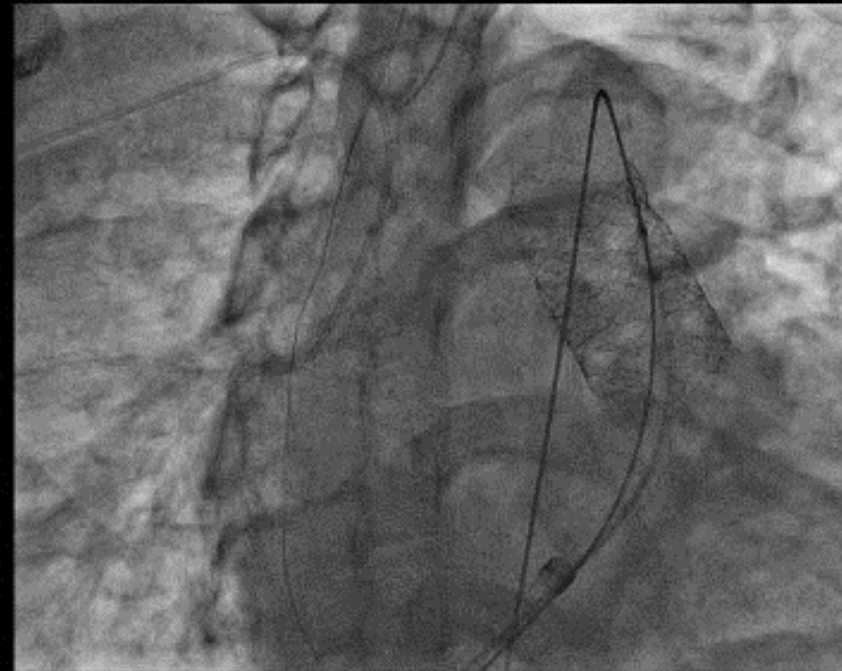
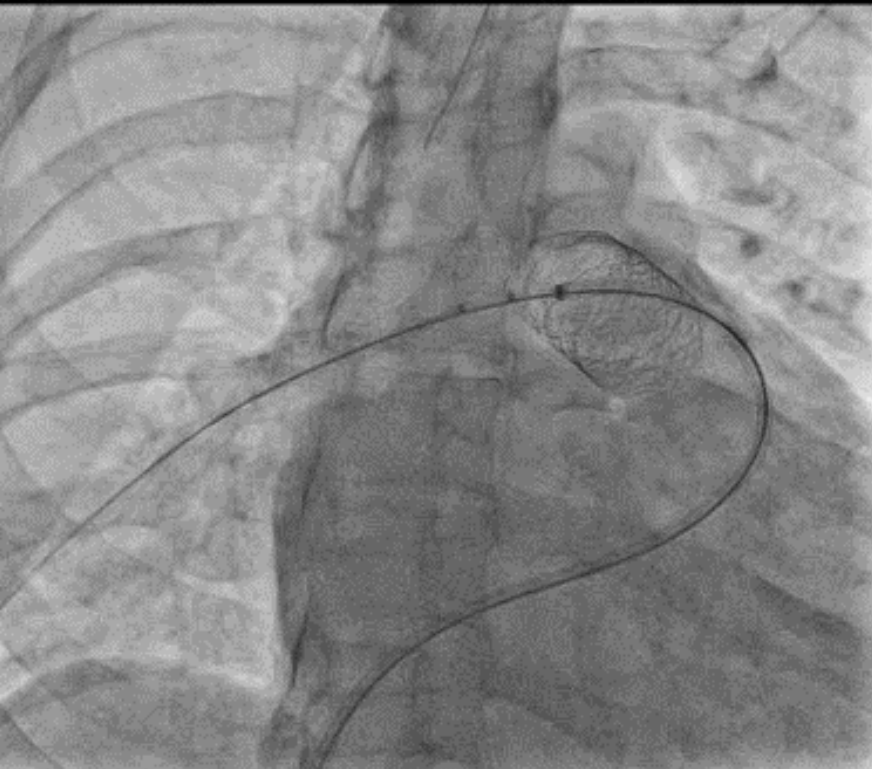
AFTER SIZING WITH 30 MM BALLOON, IMPLANTATION OF A 57 MM XXL ANDRASTENT

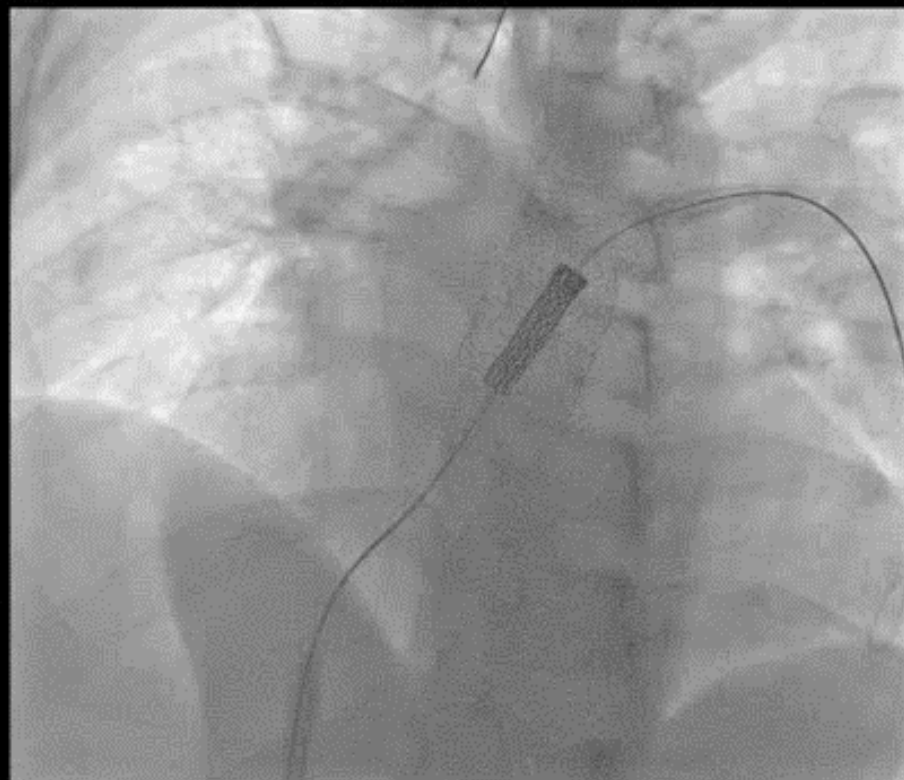
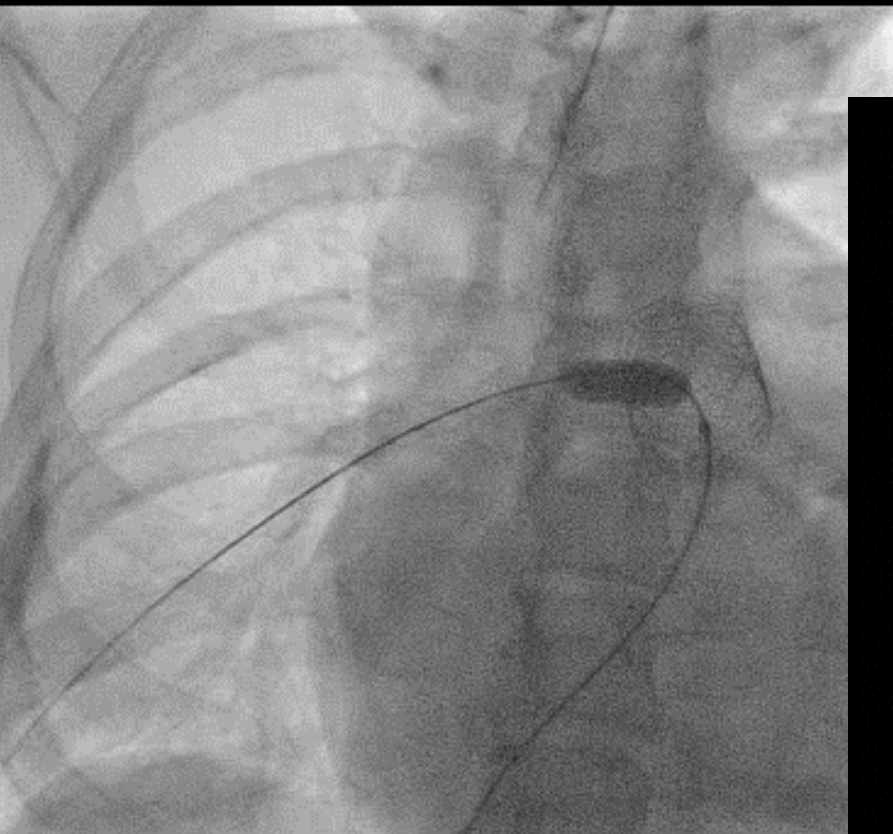


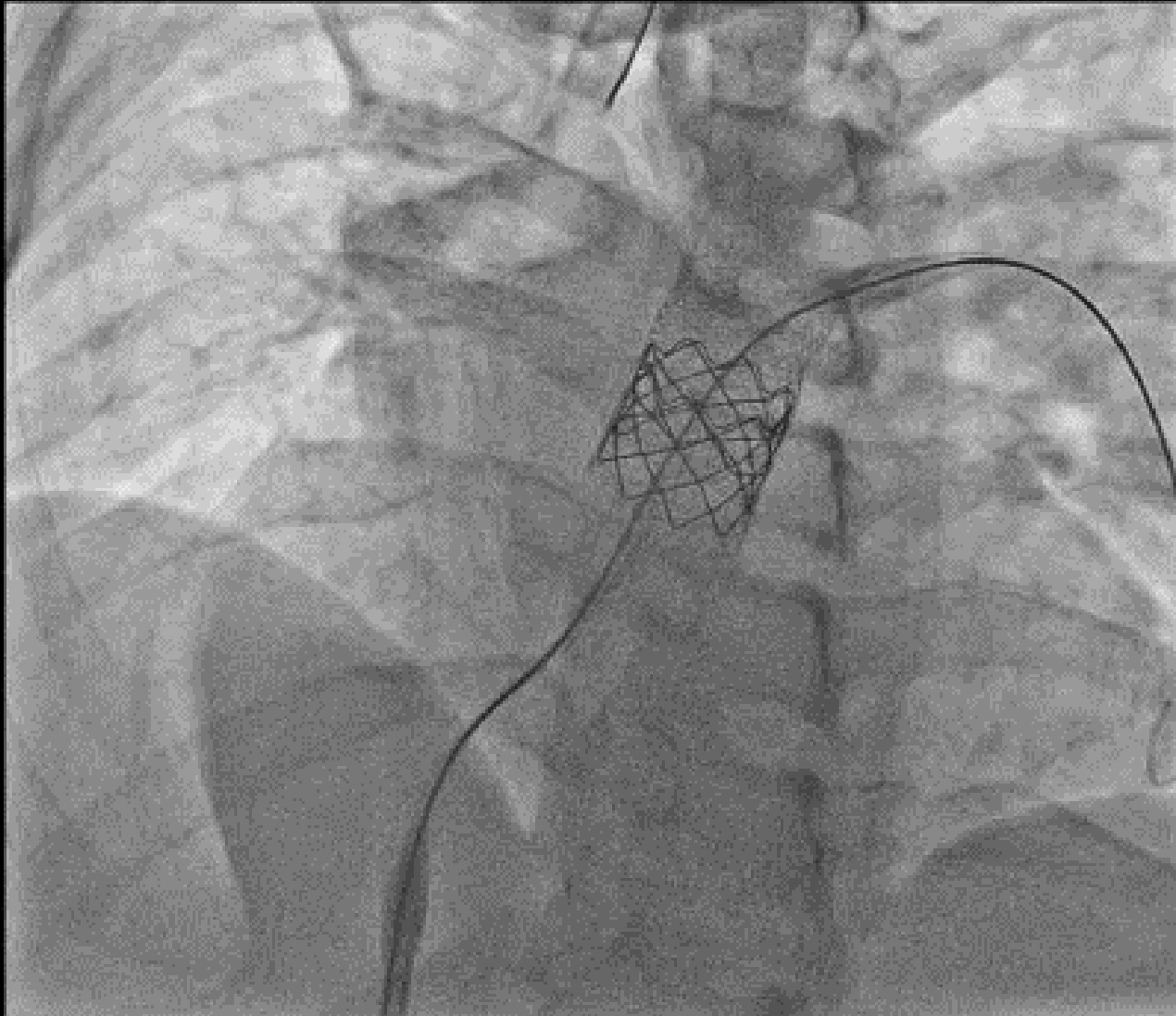
JAILING TECHNIQUE IN A 45 YO PT WITH SEVERE RV DYSFUNCTION







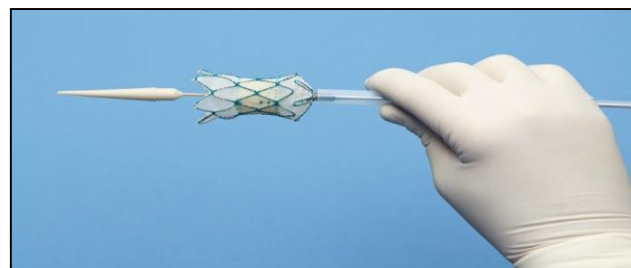
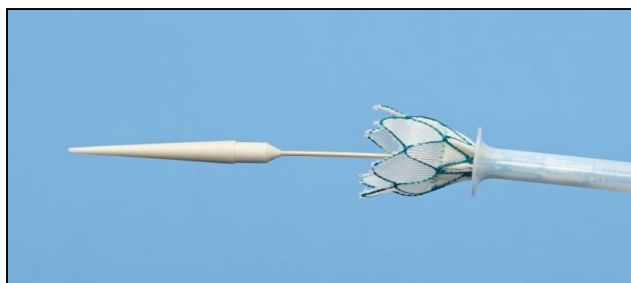
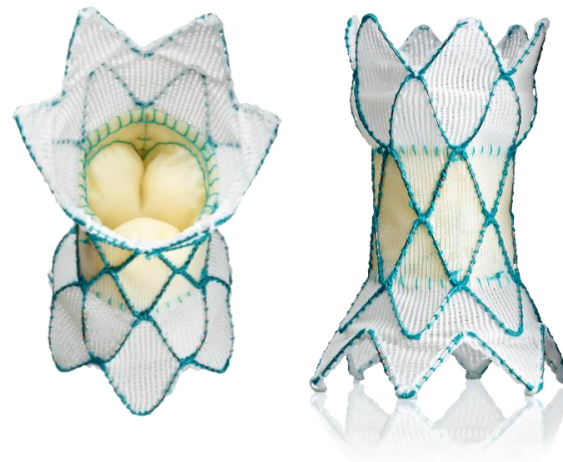




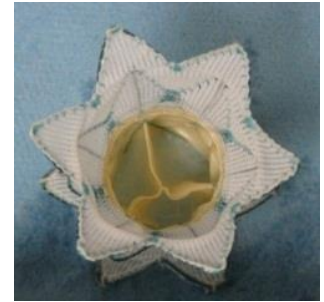
HARMONY™ TPV

Porcine Pericardial Tissue Valve

- 22mm ID
- AOA treated tissue
- Tissue valve mounted on self-expanding nitinol frame with polyester cloth covering



BACKGROUND | STUDY OVERVIEW



Prospective, Non-randomized

- Primary Objective:
 - *Obtain in vivo data to confirm assumptions on loading conditions for future in vitro frame evaluations*
- Secondary Objectives:
 - *Characterize procedural feasibility, safety & TPV performance*
- 20 patients implanted for 5 year follow-up at 3 centers (May 2013 – May 2015)
 - The Hospital for Sick Children, Toronto Canada – Dr. Lee Benson
 - Nationwide Children's Hospital, Columbus Ohio – Dr. John Cheatham
 - Boston Children's Hospital, Boston, MA – Drs. Jim Lock & Lisa Bergersen
- DSMB to Monitor the Study
- Screening Committee review of all potential candidates

HARMONY™ TPV



Learning from

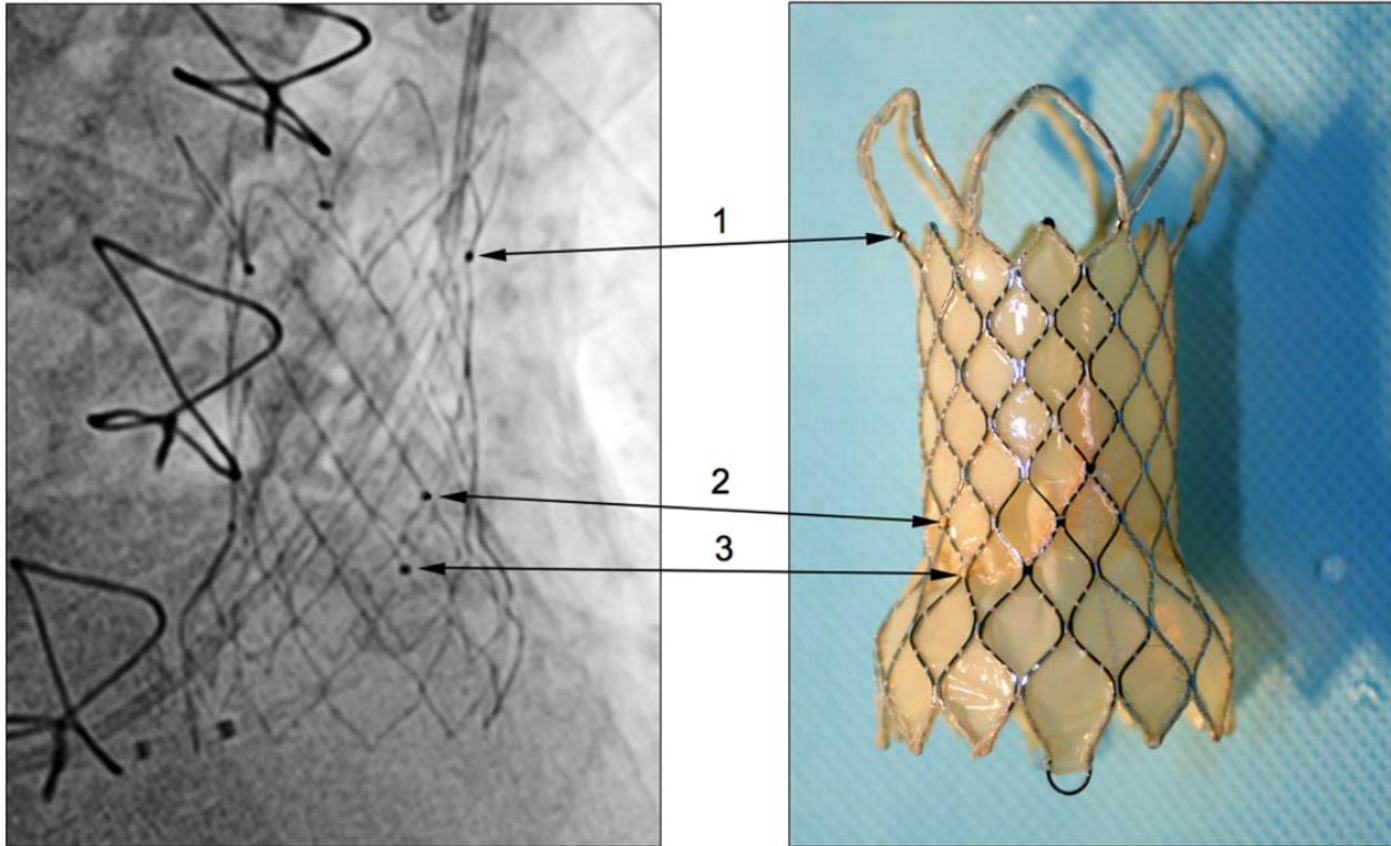
Early Feasibility Study

- The first ever FDA approved EFS was successful
- The Harmony TPV restores pulmonary valve function in patients with severe PR
- Designing appropriate valve frames will be challenging, but we now have a method to do it
- Appropriate selection of patients will be critical in the continued success of treating the larger RVOT population

What's Next?

- Continued follow-up and assessment of Early Feasibility Study patients
- Analysis of data from >300 patients
- Optimization of system design
- Refine patient selection / screening / imaging protocols for future studies and commercialization
- Refine procedural development and training guidelines
- *One-year data at TCT 2016*
- *IDE study approved by FDA*
 - *First implant – Early 2017*

VENUS P VALVE FOR LARGE RVOT



Structure (stent): Nitinol self-expandable "
•! Integrated, unidirectional tri-leaflet porcine "
" pericardial tissue valve"

CONCLUSIONS

- Larger options for transcatheter pulmonary valve implantation, especially considering « off label » indications
- Need for more follow-up and comparison with surgery for long-term outcome
- Efficiency and outcome for valve-in-valve implantation?