SUPPLEMENTAL MATERIAL to

Long-Term Outcomes After Melody Transcatheter Pulmonary Valve Replacement in the U.S. Investigational Device Exemption Trial

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Supplemental Figures and Figure Legends

Figure S1. Patient Flow. Patient flow is depicted on the left. Cumulative patient exits are depicted in the column on the right. Patients were initially enrolled for 5 years or until the TPV was explanted. Two years after the final implant, the study protocol was modified. All active patients were approached to consent to an additional 5 years of follow-up (10 years total). Those who did not consent to longer-term follow-up, exited the study at that time (noted as "study completed"). EXP = explanted; W/D = withdrew; LTFU = lost to follow-up; Comp = study completed.

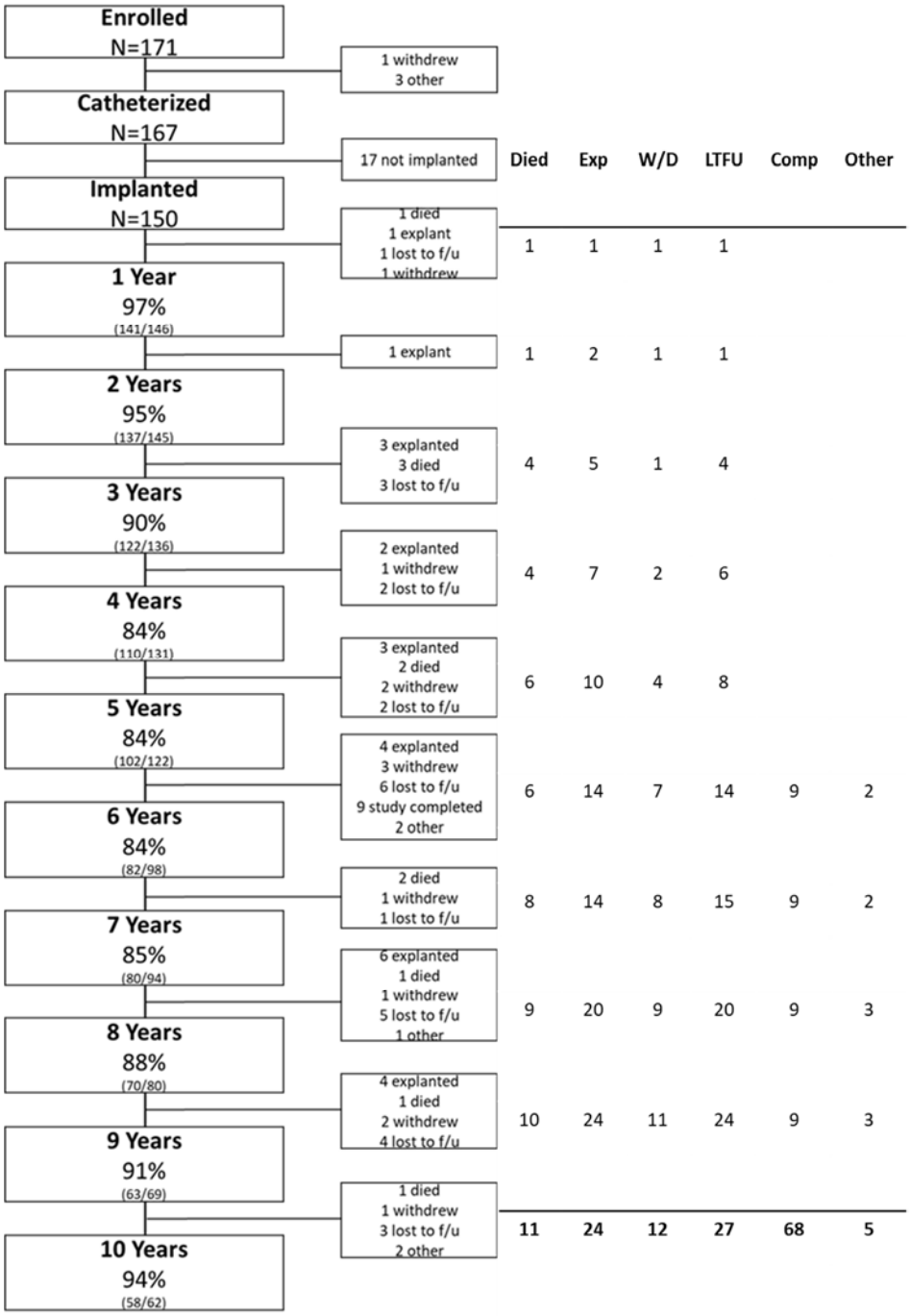
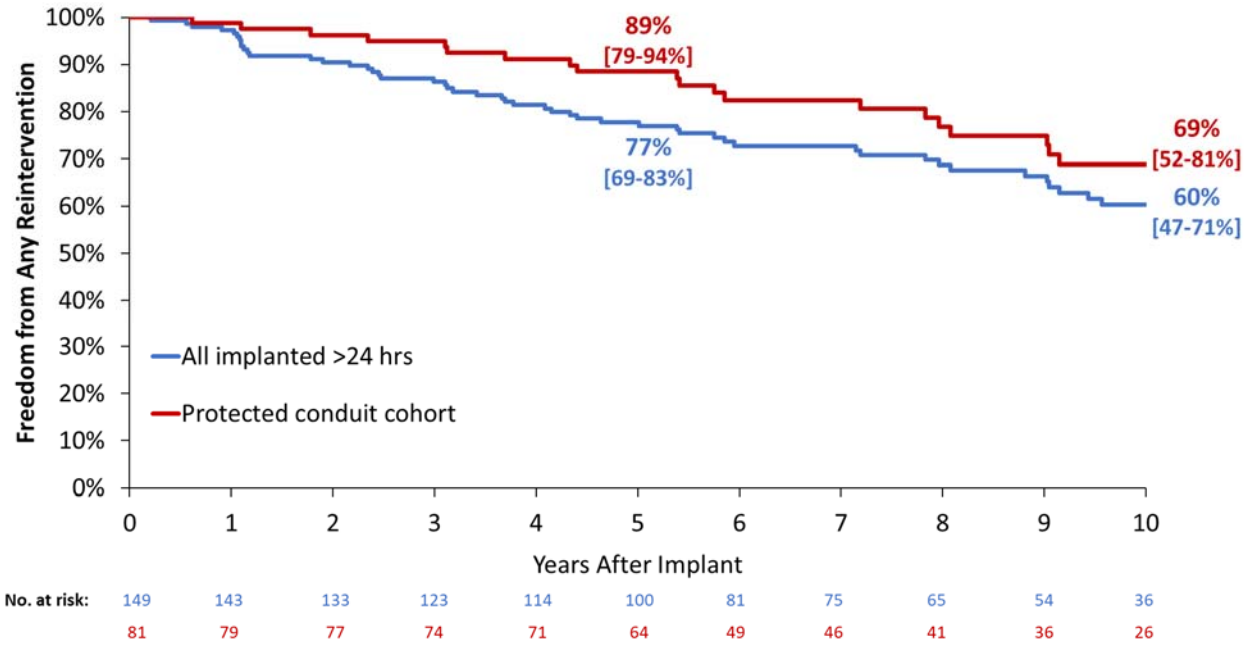
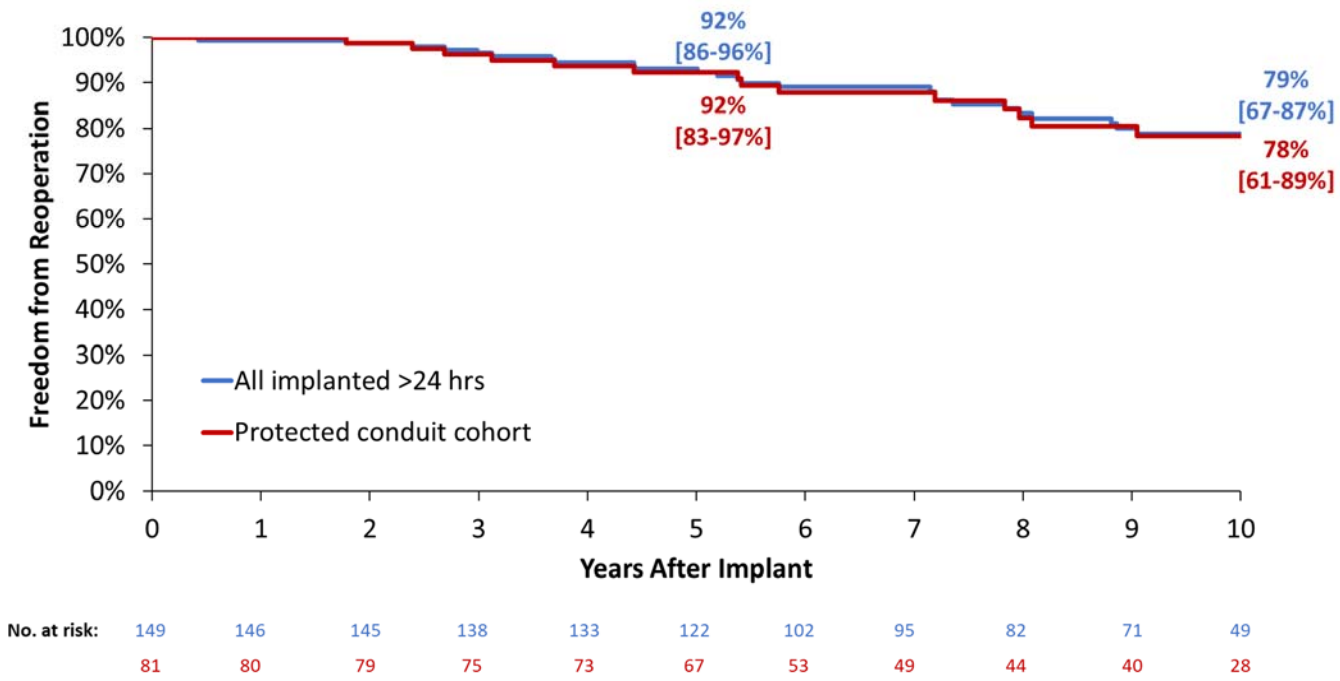


Figure S2. These Kaplan-Meier curves depict A) Freedom from any reintervention (all implanted vs. protected); B) Freedom from reoperation (all implanted vs. protected); A) Freedom from reintervention by age group. Kaplan-Meier event rates with [95% confidence intervals] are reported. Endpoint evaluated in patients implanted >24 hours. In (A) and (B), groups are not mutually exclusive.

A)



B)



C)

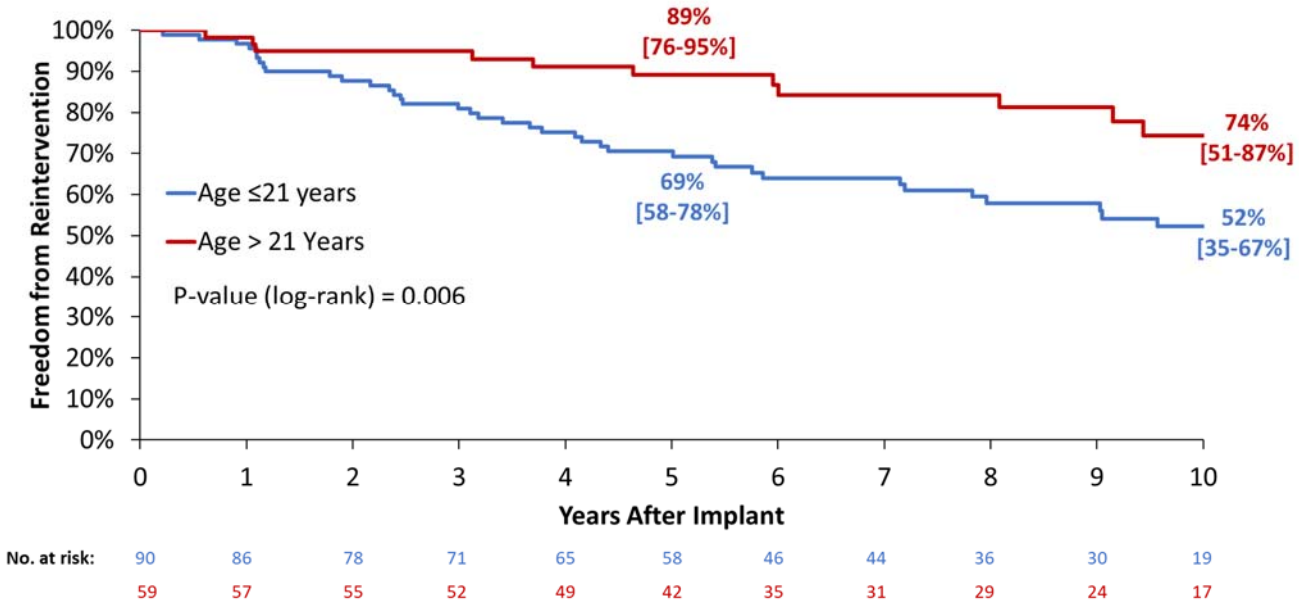
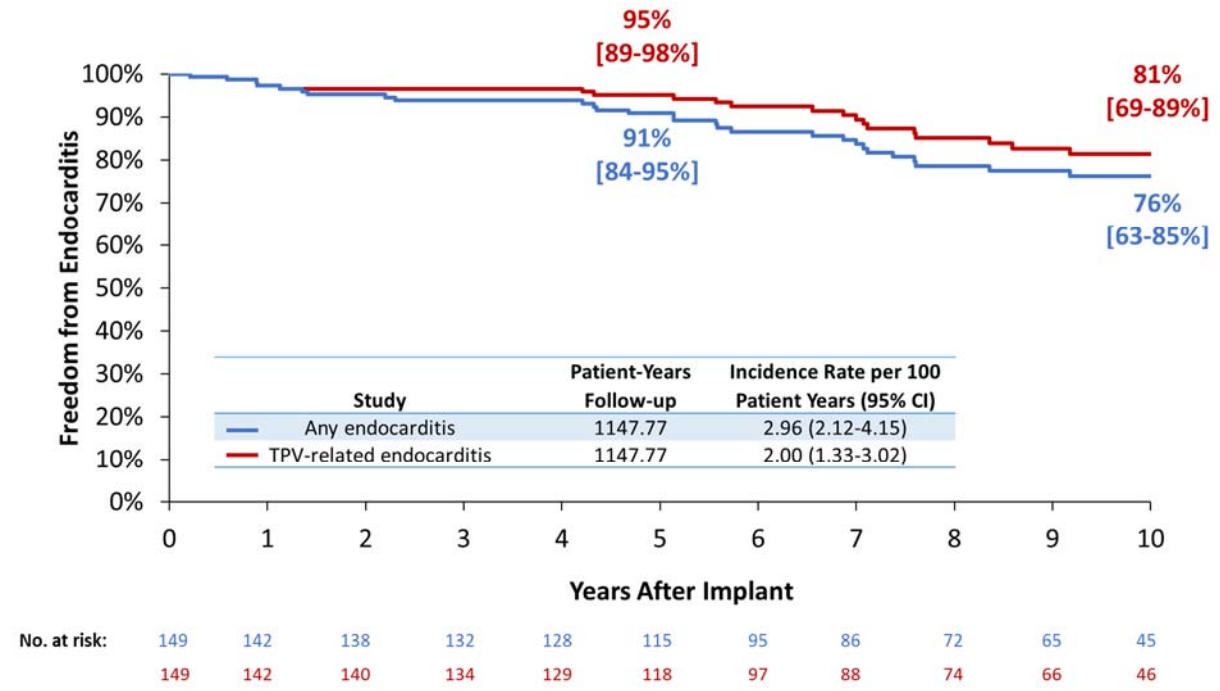
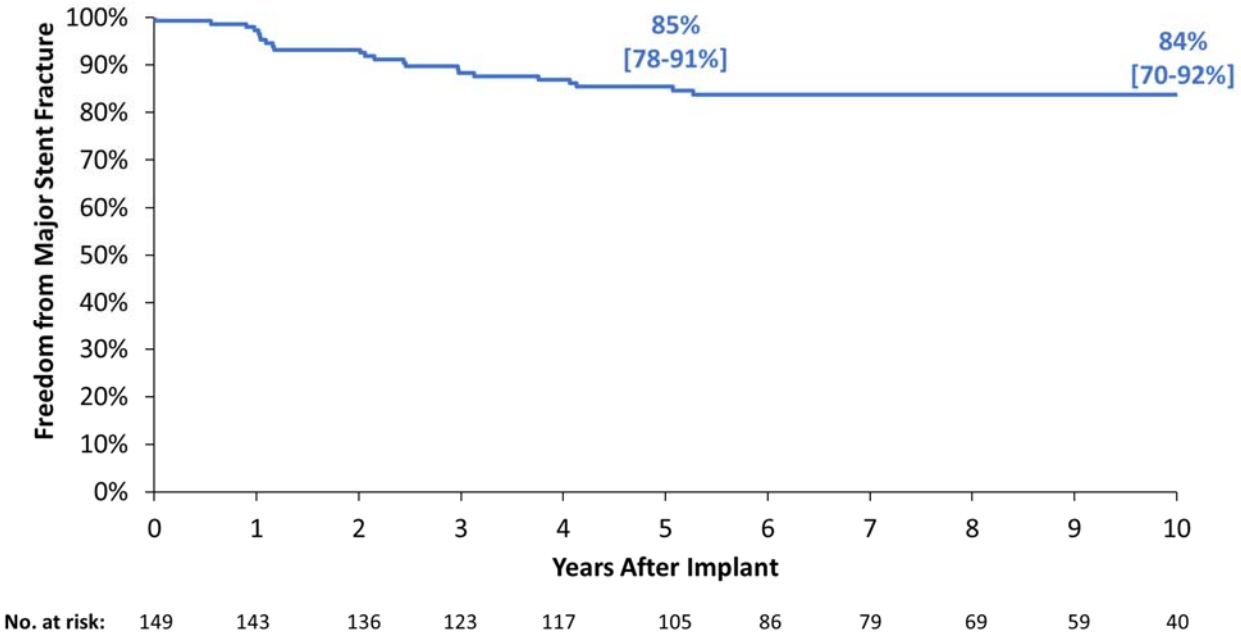

89%
[76-95%]
74%
[51-87%]
69%
[58-78%]
52%
[35-67%]
Age ≤21 years
Age > 21 Years
P-value (log-rank) = 0.006
Freedom from Reintervention
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
9
10
Years After Implant
No. at risk:
90 86 78 71 65 58 46 44 36 30 19
59 57 55 52 49 42 35 31 29 24 17

Figure S3. Kaplan-Meier curves depicting A) Freedom from endocarditis. Endocarditis was defined according to the modified Duke criteria; B) Freedom from major stent fracture, which was defined as a fracture requiring intervention to prevent permanent impairment of a body function or permanent damage to a body structure. Endpoint evaluated in patients implanted >24 hours. Rates are displayed with [95% confidence intervals].

A)



B)



Supplemental Tables

Table S1. Inclusion and Exclusion Criteria

Inclusion Criteria • Age ≥5 years of age • Weight ≥30 kilograms • Existence of a full (circumferential) RVOT conduit that was ≥16 mm in diameter when originally implanted, or a stented bioprosthesis with a rigid circumferential sewing ring in the RVOT that has an internal diameter ≥18 mm and ≤22 mm when originally implanted • Any of the following by transthoracic echocardiography For patients in NYHA Classification II, III, or IV: Moderate (3+) or severe (4+) pulmonary regurgitation, or Mean RVOT gradient ≥35 mmHg. For patients in NYHA Classification I: Severe (4+) pulmonary regurgitation with RV dilatation or dysfunction, or Mean RVOT gradient ≥40 mmHg.
Exclusion Criteria • Active endocarditis • A major or progressive non-cardiac disease (e.g. liver failure, renal failure, cancer) that results in a life expectancy of <1 year • Patient or guardian unwilling or unable to provide written informed consent or comply with follow-up requirements • Obstruction of the central veins (including the superior and inferior vena cava, bilateral iliac veins) such that the delivery system cannot be advanced to the heart via transvenous approach from either femoral vein or internal jugular vein • Positive urine or serum pregnancy test 24 hours prior to procedure in female patients of child bearing potential • Known intravenous drug abuse

Table S2. Baseline characteristics for all patients, patients implanted under the updated protocol, patients with a protected conduit, and according to the primary implant indication

Variable	All Implanted Patients (N=150)	Updated Protocol Cohort (after pre-stenting allowed) (N=115)	Protected Conduit Cohort (N=81)	Primary Implant Indication		
				Regurgitation (N=80)	Mixed (N=31)	Stenosis (N=39)
Male	96 (64%)	70 (61%)	48 (59%)	49 (61%)	19 (61%)	28 (72%)
Age (years)	19 (15, 26)	19 (14, 29)	21 (14, 31)	21 (16, 29)	17 (14, 23)	17 (14, 24)
≤21years old	90 (60%)	65 (57%)	44 (54%)	41 (51%)	23 (74%)	26 (67%)
>21 years old	60 (40%)	50 (44%)	37 (46%)	39 (49%)	8 (26%)	13 (33%)
Weight (kg)	63 (51, 76)	63 (50, 78)	62 (50, 74)	64 (56, 77)	60 (45, 71)	63 (47, 79)
Original Diagnosis						
Tetralogy of Fallot	77 (51%)	58 (50%)	42 (52%)	49 (61%)	15 (48%)	13 (33%)
Aortic valve disease (Ross)	31 (21%)	26 (23%)	12 (15%)	12 (15%)	5 (16%)	14 (36%)
Truncus arteriosus	15 (10%)	10 (9%)	9 (11%)	5 (6%)	4 (13%)	6 (15%)
Transposition of the Great Arteries	16 (11%)	13 (11%)	13 (16%)	7 (9%)	5 (16%)	4 (10%)
Other Diagnosis	11 (7%)	8 (7%)	5 (6%)	7 (9%)	2 (7%)	2 (5%)
NYHA						
I	21 (14%)	14 (12%)	10 (12%)	6 (8%)	3 (10%)	12 (31%)
II	104 (69%)	81 (70%)	56 (69%)	55 (69%)	26 (84%)	23 (59%)
III	24 (16%)	19 (17%)	15 (19%)	18 (23%)	2 (7%)	4 (10%)
IV	1 (1%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)

Variable	All Implanted Patients (N=150)	Updated Protocol Cohort (after pre-stenting allowed) (N=115)	Protected Conduit Cohort (N=81)	Primary Implant Indication		
				Regurgitation (N=80)	Mixed (N=31)	Stenosis (N=39)
# of previous open-heart surgeries	2 (2, 3)	2 (2, 3)	2 (2, 3)	2 (2, 3)	2 (1, 3)	2 (2, 3)
RVOT conduit type						
Homograft	109 (73%)	81 (70%)	45 (56%)	55 (69%)	23 (74%)	31 (80%)
Biological valved conduit	19 (13%)	16 (14%)	19 (24%)	11 (14%)	2 (7%)	6 (15%)
Bioprosthesis within the RVOT	11 (7%)	10 (9%)	11 (14%)	7 (9%)	3 (10%)	1 (3%)
Other	11 (7%)	8 (7%)	6 (7%)	7 (9%)	3 (10%)	1 (3%)
Primary Indication						
Stenosis	39 (26%)	34 (30%)	25 (31%)	0 (0%)	0 (0%)	39 (100%)
Regurgitant	80 (53%)	58 (50%)	38 (47%)	80 (100%)	0 (0%)	0 (0%)
Mixed	31 (21%)	23 (20%)	18 (22%)	0 (0%)	31 (100%)	0 (0%)
Pre-existing stent in RVOT conduit						
No pre-existing stents	113 (75%)	93 (81%)	66 (82%)	52 (65%)	22 (71%)	39 (100%)
Single stent	24 (16%)	12 (10%)	10 (12%)	18 (23%)	6 (19%)	0 (0%)
Multiple stents	13 (9%)	10 (9%)	5 (6%)	10 (13%)	3 (10%)	0 (0%)
Delivery system size (mm)						
18mm	23 (15%)	8 (7%)	6 (7%)	12 (15%)	5 (16%)	6 (15%)
20mm	41 (27%)	33 (29%)	25 (31%)	19 (24%)	11 (36%)	11 (28%)
22mm	86 (57%)	74 (64%)	50 (62%)	49 (61%)	15 (48%)	22 (56%)
Post-implant dilation performed	69 (46%)	42 (37%)	31 (38%)	35 (44%)	11 (36%)	23 (59%)

Variable	All Implanted Patients (N=150)	Updated Protocol Cohort (after pre-stenting allowed) (N=115)	Protected Conduit Cohort (N=81)	Primary Implant Indication		
				Regurgitation (N=80)	Mixed (N=31)	Stenosis (N=39)
Pre-implant peak RVOT gradient	37 (22, 47)	37 (20, 47)	39 (26, 48)	26 (16, 41)	43 (31, 50)	45 (40, 51)
Post-implant peak RVOT gradient	13 (9, 17)	11 (8, 16)	11 (8, 16)	12 (7, 17)	13 (10, 17)	14 (10, 19)
Discharge mean Doppler gradient	17 (12, 22)	17 (12, 21)	17 (12, 21)	16 (11, 21)	18 (13, 21)	20 (16, 24)
Post-implant peak gradient >15mm Hg	53 (35%)	32 (28%)	23 (28%)	23 (29%)	13 (42%)	17 (44%)
Hospital stay >1 day	15 (10%)	12 (10%)	10 (12%)	9 (11%)	2 (6%)	4 (10%)

Values are no. (%) or median (Q1, Q3).

Table S3. CPET results over time – Implanted >24 hours Cohort (N=149)

	Pre-Implant (N=121)	6-Months (N=116)	1 Year (N=114)	2 Year (N=109)	3 Year (N=88)	4 Year (N=75)	5 Year (N=70)
Peak VO2 Achieved (ml/kg/min)							
NYHA I or II	23.9 [19.4, 29.0] (119)	24.9 [19.6, 30.0] (115)	24.0 [18.1, 30.0] (114)	23.8 [19.1, 27.9] (107)	24.3 [18.6, 29.8] (88)	23.6 [20.0, 30.1] (75)	23.7 [17.7, 29.6] (69)
NYHA III or IV	15.7 [12.3, 19.6] (24)	17.6 [15.4, 21.1] (21)	16.2 [14.3, 19.9] (18)	16.5 [15.0, 19.2] (18)	16.4 [12.0, 19.9] (15)	18.3 [14.1, 20.1] (14)	17.7 [14.8, 20.1] (11)
% Predicted VO2 Achieved							
NYHA I or II	60 [48, 71] (119)	61 [51, 76] (115)	61 [47, 75] (114)	63 [50, 73] (107)	61 [47, 73] (84)	61 [51, 74] (74)	64 [52, 74] (65)
NYHA III or IV	43 [36, 57] (24)	56 [42, 71] (21)	50 [38, 63] (18)	54 [38, 62] (18)	49 [37, 70] (15)	52 [46, 66] (13)	50 [42, 63] (11)
AT (ml/kg/min)							
NYHA I or II	15.5 [11.6, 20.8] (112)	15.7 [11.8, 19.0] (111)	15.0 [11.6, 19.4] (110)	14.5 [11.7, 18.4] (103)	14.6 [11.2, 19.0] (86)	15.5 [11.5, 18.0] (74)	14.5 [11.7, 16.8] (65)
NYHA III or IV	13.3 [10.3, 15.7] (17)	12.2 [10.4, 15.2] (19)	11.0 [9.1, 12.4] (15)	10.9 [9.9, 13.1] (17)	11.3 [9.2, 14.9] (14)	12.8 [10.4, 14.6] (14)	12.3 [10.7, 14.6] (11)
% Predicted AT							
NYHA I or II	40 [33, 52] (112)	39 [32, 48] (111)	39 [30, 49] (110)	38 [31, 45] (102)	37 [28, 50] (83)	38 [32, 45] (72)	37 [31, 45] (62)
NYHA III or IV	35 [32, 41] (17)	36 [31, 54] (19)	31 [27, 43] (16)	33 [26, 40] (17)	35 [30, 43] (14)	35 [32, 43] (12)	32 [26, 48] (11)
VE/VCO2 at AT							
NYHA I or II	30 [28, 33] (112)	29 [26, 31] (111)	29 [27, 32] (110)	29 [27, 32] (103)	29 [27, 31] (86)	28 [25, 30] (72)	28 [26, 31] (64)
NYHA III or IV	35 [30, 38] (17)	30 [27, 36] (19)	31 [29, 33] (15)	30 [28, 33] (17)	31 [29, 36] (14)	30 [27, 33] (13)	29 [25, 30] (11)
RER at Peak VO2							
NYHA I or II	1.1 [1.0, 1.2] (119)	1.1 [1.1, 1.2] (115)	1.1 [1.1, 1.2] (114)	1.1 [1.1, 1.2] (107)	1.2 [1.1, 1.2] (88)	1.2 [1.1, 1.3] (73)	1.2 [1.1, 1.3] (68)

	Pre-Implant (N=121)	6-Months (N=116)	1 Year (N=114)	2 Year (N=109)	3 Year (N=88)	4 Year (N=75)	5 Year (N=70)
NYHA III or IV	1.1 [1.0, 1.2] (24)	1.2 [1.1, 1.2] (21)	1.1 [1.0, 1.2] (18)	1.1 [1.0, 1.2] (18)	1.1 [1.0, 1.2] (15)	1.1 [1.1, 1.2] (14)	1.1 [1.1, 1.2] (11)
% Predicted Forced Vital Capacity (FVC)							
NYHA I or II	80 [69, 91] (118)	79 [70, 93] (115)	81 [69, 94] (113)	82 [71, 94] (104)	84 [70, 97] (87)	81 [72, 95] (75)	80 [69, 94] (69)
NYHA III or IV	65 [40, 79] (24)	72 [39, 85] (21)	65 [38, 83] (18)	73 [40, 81] (18)	63 [39, 78] (15)	67 [42, 78] (14)	63 [44, 82] (11)
% Predicted Forced Expiration Volume (1 sec)							
NYHA I or II	77 [64, 90] (118)	81 [67, 92] (115)	82 [67, 91] (113)	80 [67, 92] (104)	83 [66, 92] (87)	82 [65, 94] (75)	80 [67, 89] (69)
NYHA III or IV	56 [40, 76] (24)	68 [37, 77] (21)	59 [35, 79] (18)	64 [37, 73] (18)	53 [38, 68] (15)	56 [36, 76] (14)	55 [46, 74] (11)
Peak Heart Rate							
NYHA I or II	157 [144, 173] (121)	159 [144, 174] (116)	158 [137, 173] (114)	160 [135, 172] (108)	155 [141, 176] (88)	162 [145, 173] (75)	154 [132, 180] (70)
NYHA III or IV	132 [122, 161] (24)	146 [125, 158] (21)	131 [116, 158] (18)	133 [108, 148] (18)	129 [126, 148] (15)	135 [126,162] (14)	141 [126, 162] (11)
Peak Workload							
NYHA I or II	115 [76, 148] (120)	124 [81, 160] (116)	121 [87, 159] (114)	122 [97, 162] (106)	132 [101, 175] (88)	136 [103, 182] (75)	136 [102, 176] (69)
NYHA III or IV	73 [51, 107] (24)	92 [68, 116] (21)	73 [58, 123] (18)	76 [60, 119] (18)	73 [47, 120] (15)	76 [65, 115] (14)	88 [71, 135] (10)
Peak Oxygen Pulse							
NYHA I or II	9.0 [7.0, 12.0] (119)	10.0 [7.0, 12.0] (115)	10.0 [7.0, 12.0] (114)	10.0 [8.0, 12.5] (108)	10.7 [8.0, 13.8] (88)	10.3 [8.1, 14.0] (75)	11.0 [8.3, 14.0] (69)
NYHA III or IV	7.5 [6.5, 10.5] (24)	9.0 [7.0, 11.0] (21)	8.0 [7.0, 11.0] (18)	8.0 [7.0, 12.7] (18)	7.9 [6.3, 9.5] (15)	8.0 [6.5, 11.0] (14)	9.0 [6.0, 11.0] (11)
% Predicted Peak Expiratory Flow Rate							
NYHA I or II	79 [59, 96] (112)	80 [60, 95] (115)	80 [64, 99] (111)	82 [63, 95] (104)	82 [65, 94] (87)	86 [67, 96] (74)	82 [61, 93] (68)

	Pre-Implant (N=121)	6-Months (N=116)	1 Year (N=114)	2 Year (N=109)	3 Year (N=88)	4 Year (N=75)	5 Year (N=70)
NYHA III or IV	62 [44, 81] (23)	63 [54, 80] (21)	61 [45, 75] (18)	67 [49, 74] (18)	56 [45, 72] (15)	58 [52, 83] (14)	58 [50, 76] (11)

Values are median [Q1, Q3] (n).

Table S4.

Pre-implant and 6-month site CMR imaging data in patients implanted >24 hours

	PR Indication			Mixed Indication			Stenosis Indication		
Variable[1]	Pre-implant	6 Months	P value	Pre-implant	6 Months	P value	Pre-implant	6 Months	P value
PR Fraction (%)	35 (26, 43) [50]	0.0 (0.0, 2.8) [52]	<0.001	16 (12, 28) [26]	1.2 (0.0, 2.6) [22]	<0.001	7.9 (0.7, 15) [30]	1.1 (0.0, 3.2) [33]	0.005
RVEDV (ml)	215 (168, 285) [59]	174 (143, 222) [56]	<0.001	186 (152, 249) [27]	167 (130, 187) [24]	<0.001	181 (130, 214) [33]	152 (126, 200) [34]	0.003
RVEDV Index (ml/m^2)	128 (108, 169) [59]	101 (85, 133) [56]	<0.001	119 (104, 148) [27]	99 (83, 124) [24]	<0.001	97 (82, 123) [33]	94 (75, 109) [33]	0.001
RVEF (%)	51 (43, 58) [59]	48 (41, 57) [56]	0.064	46 (37, 60) [27]	53 (44, 58) [24]	0.107	51 (45, 55) [33]	52 (45, 59) [33]	0.77
LVEDV (ml)	130 (105, 172) [58]	151 (125, 181) [53]	0.001	130 (94, 158) [27]	141 (116, 170) [24]	0.021	139 (102, 168) [33]	166 (110, 179) [34]	0.001
LVEDV Index (ml/m^2)	80 (68, 96) [58]	88 (76, 98) [53]	0.007	78 (69, 91) [27]	89 (78, 101) [24]	0.049	80 (66, 95) [33]	90 (71, 98) [33]	0.005
LVEF (%)	58 (52, 62) [58]	59 (54, 63) [53]	0.386	56 (50, 62) [27]	58 (54, 64) [24]	0.220	63 (57, 69) [33]	62 (59, 67) [34]	0.90

[1]Data after TPV-in-TPV or explant are excluded.

Values are median (Q1, Q3) [n]. P values reflect paired comparisons.