

Acute and midterm outcomes of the post-approval MELODY Registry: a multicentre registry of transcatheter pulmonary valve implantation

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Aims

The post-approval MELODY Registry aimed to obtain multicentre registry data after transcatheter pulmonary valve implantation (TPVI) with the Melody™ valve (Medtronic plc.) in a large-scale cohort of patients with congenital heart disease (CHD).

Methods and results

Retrospective analysis of multicentre registry data after TPVI with the Melody™ valve. Eight hundred and forty-five patients (mean age: 21.0 ± 11.1 years) underwent TPVI in 42 centres between December 2006 and September 2013 and were followed-up for a median of 5.9 years (range: 0–11.0 years). The composite endpoint of TPVI-related events during follow-up (i.e. death, reoperation, or reintervention >48 h after TPVI) showed an incidence rate of 4.2% per person per year [95% confidence interval (CI) 3.7–4.9]. Transcatheter pulmonary valve implantation infective endocarditis (I.E.) showed an incidence rate of 2.3% per person per year (95% CI 1.9–2.8) and resulted in significant morbidity and in nine deaths. In multivariable Cox proportional hazard models, the invasively measured residual right ventricle (RV)-to-pulmonary artery (PA) pressure gradient (per 5 mmHg) was associated with the risk of the composite endpoint (adjusted hazard ratio: 1.21, 95% CI 1.12–1.30; $P < 0.0001$) and the risk of TPVI I.E. (adjusted hazard ratio: 1.19, 95% CI 1.07–1.32; $P = 0.002$). Major procedural complications (death, surgical, or interventional treatment requirement) occurred in 0.5%, 1.2%, and 2.0%, respectively. Acutely, the RV-to-PA pressure gradient and the percentage of patients with pulmonary regurgitation grade >2 improved significantly from 36 [interquartile range (IQR) 24–47] to 12 (IQR 7–17) mmHg and 47 to 1%, respectively ($P < 0.001$ for each).

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Conclusion

The post-approval MELODY Registry confirms the efficacy of TPVI with the Melody™ valve in a large-scale cohort of CHD patients. The residual invasively measured RV-to-PA pressure gradient may serve as a target for further improvement in the composite endpoint and TPVI I.E. However, TPVI I.E. remains a significant concern causing significant morbidity and mortality.

Keywords

Congenital heart disease • Transcatheter pulmonary valve implantation • RVOT dysfunction

Introduction

Transcatheter pulmonary valve implantation (TPVI) plays an important role within current treatment strategies for patients with congenital heart disease (CHD) and right ventricular outflow tract (RVOT) dysfunction.^{1–9} Right ventricular outflow tract dysfunction frequently occurs in these patients because of the limited lifespan of the material that was used during surgical repair.

Currently, two balloon-expandable devices are available for TPVI: the Melody™ valve (Medtronic plc, Ireland; CE-mark approval in 2006) and the SAPIEN XT (Edwards Lifesciences LLC, USA; FDA-approval in 2017). The devices have different specifications related to the intended TPVI diameters (Melody valve™: 18, 20, and 22 mm; SAPIEN XT: 20, 23, 26, and 29 mm).

The post-approval MELODY Registry aimed to obtain multicentre registry data after TPVI with the Melody™ valve in a large-scale cohort of patients with CHD.

Methods

Study design

The post-approval MELODY Registry is an investigator-initiated, multicentre registry after TPVI with the Melody™ valve outside the USA. Participating centres were approached during Melody™ valve implanters meetings in Europe, regardless of the implanting physician's level of past experience with TPVI. This strategy was adopted to achieve a large number of included patients and to allow for an assessment of observational data obtained in routine clinical practice. Overall, 42 cardiac centres contributed data of patients who received TPVI with the Melody™ valve after CE-mark approval.

In this study, patients were registered retrospectively. Firstly, study centres submitted anonymized data on patients who underwent TPVI with the Melody™ valve in the pulmonary position during the study period ($n = 1080$). Secondly, during computerized data management that was performed by the Coordination Center of Clinical Studies (KKS, Charité University Medicine Berlin), specified exclusion criteria were applied to allow for a consistent dataset that would be amenable for further statistical analysis (Supplementary material online, Figure S1). Thus, 845/1080 datasets (78.2%) were included for analysis.

The study adhered to international rules for scientific studies and the Helsinki principles. Consent was given by patients and/or parents/guardians as appropriate. The institutional review board or ethics committee at participating centres approved the submission of data. The events and values collected were site reported, and there were no core laboratories. The coordinating centre of the MELODY Registry was the German Heart Institute Berlin, Germany, where the data were collected and analysed. The decision to undergo TPVI with the Melody™ valve was made

at each participating centre's discretion reflecting international guidelines.¹⁰

General inclusion and exclusion criteria for TPVI with the Melody™ valve as well as details of the implantation procedure have been described previously.^{1–9}

Endpoints

Primary endpoints

Primary endpoints of the study included a composite endpoint of TPVI-related follow-up events (i.e. death, reoperation, or reintervention >48 h after TPVI) and TPVI infective endocarditis (I.E.) according to modified Duke criteria (possible or definite).^{11–14}

Secondary endpoints

Secondary endpoints of the study included procedural complications of TPVI with the Melody™ valve (i.e. any adverse event that occurred during the procedure or ≤48 h after TPVI), invasive assessment of acute haemodynamic changes after TPVI with the Melody™ valve and non-invasive follow-up assessment up to 10–14 months after TPVI (labelled '1 year'). Non-invasive follow-up assessment was performed according to each institution's routine practice and not in a protocol-specified manner; no dates of assessment were recorded. Usually, patients were assessed within 1–3 months post-TPVI (labelled 'post') and within 10–14 months after TPVI (labelled '1 year'). The exam techniques that were applied during the non-invasive follow-up assessment included echocardiography, clinical assessment [New York Heart Association (NYHA) class], and chest X-ray investigation; more detailed information on the non-invasive follow-up assessment is provided in the Supplementary material online, Figure Legends. Presence of TPVI stent fractures were graded according to the stent fracture classification by Nordmeyer et al.,¹⁵ with the known limitations of fracture identification within multiple stent frames.

Data on the invasive assessment of acute haemodynamic changes was available for 635/845 (75%) to 826/845 (98%) patients (Table 6); data on the non-invasive follow-up assessment was available for 413/845 (49%) to 781/845 (92%) patients (Supplementary material online, Figure S4). Information on the presence of stent fractures at '1 year' was available in 633/845 (75%) patients.

Statistics

Continuous data are expressed as mean ± standard deviation or median with interquartile range (IQR) or range, while categorical data are shown as absolute and relative frequencies (percentages). Continuous data were compared using unpaired Student's *t* tests or with Mann–Whitney *U* tests where appropriate. The Kruskal–Wallis test was applied to compare more than two groups. Categorical variables were compared using the χ^2 test or a Fisher's exact test if the expected cell frequencies were <5. For procedural complications, 95% confidence intervals (CIs) of the observed relative frequencies were calculated using the method of Agresti–Coull.¹⁶ Wilcoxon signed rank tests were performed to compare dependent data. For acute haemodynamic outcomes, 95% CIs of the median of the

Table 1 Baseline characteristics

Parameters	Overall population (n = 845)
Age at TPVI (years), mean ± SD	21.0 ± 11.1
Sex (female/male), n (%)	280/565 (33/67)
Height (cm), mean ± SD	161 ± 17
Weight (kg), mean ± SD	59 ± 21
Primary haemodynamic lesion, n (%)	
Predominant pulmonary stenosis (PS) ^a	458/845 (54)
Predominant pulmonary regurgitation (PR) ^b	182/845 (22)
Mixed lesion ^c	205/845 (24)
Principal diagnosis, n (%)	
Tetralogy of Fallot (TOF)	263/845 (31)
Pulmonary atresia with VSD	154/845 (18)
Truncus arteriosus communis	92/845 (11)
TGA, pulmonary stenosis (PS), VSD	80/845 (9)
Aortic valve disease, status post Ross-operation	164/845 (20)
Double outlet right ventricle (DORV) with PS	34/845 (4)
Other/unknown	58/845 (7)
Number of previous surgeries, median (range)	2 (0–6)
Right ventricular outflow tract (RVOT), n (%)	
Native or patch-extended RVOT	46/845 (6)
Homograft conduit	567/845 (68)
Heterograft conduit	92/845 (11)
Bioprosthetic heart valve (stented)	61/845 (7)
Other/unknown	79/845 (8)
Original conduit diameter	
Homograft or heterograft conduits (mm), mean ± SD	20.3 ± 3.2
≤18 mm, n (%)	178/659 (27)
18–22 mm, n (%)	271/659 (41)
>22 mm, n (%)	142/659 (22)
Unknown, n (%)	68/659 (10)
Bioprosthetic heart valves (stented) (mm), mean ± SD	21.4 ± 3.3

VSD, ventricular septal defect; TGA, transposition of the great arteries.

^aPredominant pulmonary stenosis (PS), peak RVOT velocity ≥3.5 m/s, and pulmonary regurgitation <'moderate' on echocardiography.

^bPredominant pulmonary regurgitation (PR), peak RVOT velocity <3.5 m/s, and pulmonary regurgitation > 'moderate' on echocardiography.

^cMixed lesion, patients who did not fit either the PS or PR categories.

differences between *pre* and *post* measurements were calculated using the 'Bias corrected and accelerated method' or the 'bootstrap percentile method' in case of computational errors using 10 000 resamplings.^{17,18}

Cumulative incidence functions were created to display the time-to-first event of the composite endpoint (i.e. TPVI-related death, reoperation, and reintervention) and of TPVI I.E. accounting for 'non-TPVI related death' or 'non-TPVI right ventricular outflow tract obstruction (RVOTO)' as competing risks. Starting point for the follow-up time was the day of intervention and follow-up times were summarized using median and range. Patients who underwent a TPVI-related reintervention with balloon dilation due to other reasons than TPVI I.E. remained under follow-up for the assessment of TPVI I.E. For time-to-event outcomes, multivariable Cox proportional hazards models were created to calculate cause-specific hazards, and the assumptions of proportional hazards as well as goodness-of-fit were verified. Covariates for the multivariable models included calendar year of intervention, patient age and gender, primary haemodynamic lesion, pre-stenting, size of delivery system, and

the invasively measured residual right ventricle (RV)-to-pulmonary artery (PA) pressure gradient (per 5 mmHg). Further, linear regression was done to examine the relationship between original conduit size and the intended size of the delivered TPVI (i.e. size of the EnsembleTM delivery system). For all tests, a *P*-value of <0.05 was considered statistically significant although results are to be considered as exploratory. Statistical analysis was performed on the SAS software (Version 9.4; SAS Institute Inc., Cary, NC, USA), R (Version 3.5.0 including the packages *survival*, *survminer*, and *survMisc*), and GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA).

Results

Patient characteristics

Baseline data are presented in Table 1. Between December 2006 and September 2013, 845 patients underwent TPVI with the MelodyTM

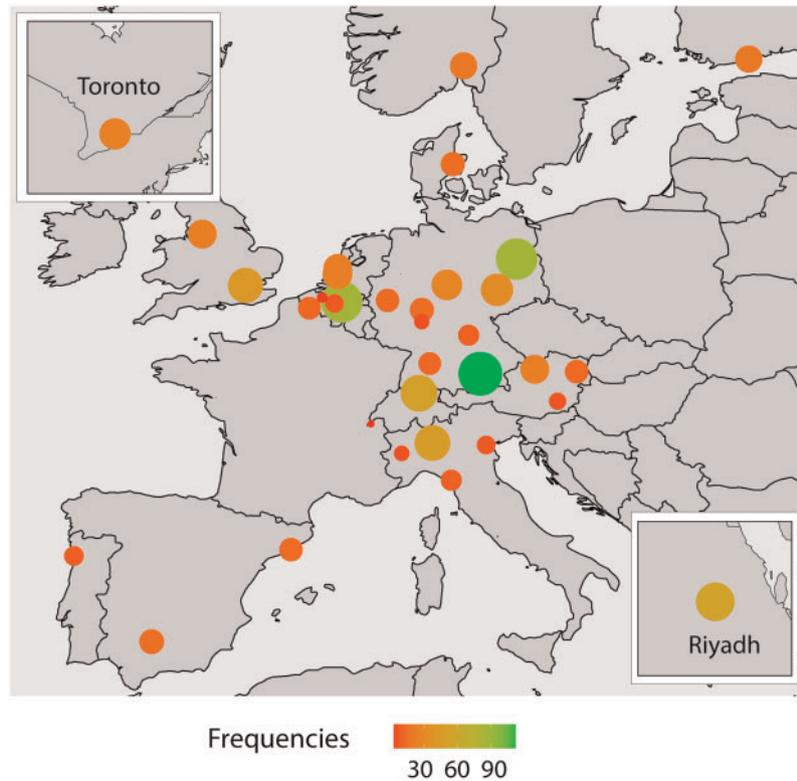


Figure 1 Geographical distribution of the study centres, including colour-coding of the sample size per study centre.

valve (Supplementary material online, Figure S2) and were followed-up for a median of 5.9 years (range 0 days to 11 years). Patients were enrolled from 42 centres (Figure 1), of which 27 centres enrolled <20 patients and 15 centres ≥ 20 .

Procedural details

Details on the procedural variables are summarized in Table 2. Pre-stenting with at least one bare metal stent prior to TPVI was performed in the majority of patients (737/845, 87%). In patients who underwent TPVI with the Melody™ valve between the years 2006 and 2009 ($n=363$), pre-stenting was used in 272/363 (74.9%) patients, whilst in the more current years (2010–2013; $n=482$), pre-stenting was used in 465/482 (96.5%) patients ($P<0.001$). On average, the pre-stenting procedure added 28 min to the overall procedure time and 5 min to the overall fluoroscopy time when compared with patients who underwent TPVI only (Supplementary material online, Tables S1 and S2). Over half Melody™ valves were implanted on a 22-mm Ensemble™ delivery system (452/845, 53.5%). The relationship between the intended size of delivered TPVI (i.e. size of Ensemble™ delivery system) and the original conduit diameter is displayed in Supplementary material online, Figure S3.

Primary endpoints

Composite endpoint

The composite endpoint of TPVI-related death, reoperation, and reintervention showed an incidence rate of 4.2% per person per year

(95% CI 3.7–4.9). The corresponding cumulative incidence plot is presented in Figure 2.

Tabulated information on the composite endpoint events can be found in Supplementary material online, Table S4. A composite endpoint event occurred in 207/845 (24.5%) patients during follow-up: there were 5/845 (0.6%) deaths due to fulminant endocarditis, 80/845 (9.5%) reoperations with TPVI explantation (TPVI I.E., $n=53$; stenosis of the Melody valve™, $n=20$; major TPVI stent fractures, $n=6$; chronic pericardial effusion, $n=1$), and 122/845 (14.4%) reinterventions (pulmonary restenosis, $n=88$; major TPVI stent fracture, $n=18$; TPVI I.E., $n=16$), of which 72/122 (59%) related to balloon dilation of TPVI and 50/122 (41%) to repeat TPVI as ‘valve-in-valve’ procedures.

In a multivariable Cox proportional hazard model (Table 3), four covariates showed a statistically significant association to the composite endpoint of TPVI-related follow-up events: patient age (adjusted hazard ratio: 0.96, 95% CI 0.95–0.98; $P=0.0001$), patient gender: female (adjusted hazard ratio: 0.67, 95% CI 0.49–0.93; $P=0.015$), size of delivery system: 22 mm (vs. 18-mm) (adjusted hazard ratio: 0.59, 95% CI 0.41–0.86; $P=0.006$), and residual RV-to-PA pressure gradient (per 5 mmHg) (adjusted hazard ratio: 1.21, 95% CI 1.12–1.30; $P<0.0001$).

Transcatheter pulmonary valve implantation infective endocarditis

Transcatheter pulmonary valve implantation I.E. showed an incidence rate of 2.3% per person per year (95% CI 1.9–2.8). The corresponding cumulative incidence plot is presented in Figure 3.

Table 2 Procedural variables

Procedural variables	Overall population (n = 845)
Procedure time (min), mean ± SD	152 ± 56
Fluoroscopy time (min), mean ± SD	32 ± 19
Vascular access route, n (%)	
Transfemoral	805/845 (95)
Transjugular	36/845 (4.5)
Other/unknown	4/845 (0.5)
Assessment of the relationship between coronary anatomy and RVOT, n (%)	
Performed prior to the TPVI catheterization procedure	87/845 (11)
Performed during the TPVI catheterization procedure	758/845 (89)
Assessment with only one modality	345/758 (46)
Assessment with combinations of modalities	413/758 (54)
Modalities used for assessment, n (%)	
Aortic root angiography	642/758 (85)
Selective coronary angiography (SCA)	392/758 (52)
SCA plus balloon inflation in RVOT ^a	281/758 (37)
Balloon sizing of RVOT, n (%)	289/845 (34)
High-pressure pre-dilation of RVOT, n (%)	405/845 (48)
Pre-stenting prior to TPVI, n (%)	
No pre-stent	108/845 (13)
1 pre-stent	555/845 (66)
2 pre-stents	148/845 (17)
3 pre-stents	34/845 (4)
Size of Ensemble delivery system (EDS) for TPVI, n (%)	
18 mm	156/845 (18)
20 mm	237/845 (28)
22 mm	452/845 (54)
High-pressure post-dilation of TPVI, n (%)	540/845 (64)
Additional procedures during catheterization ^b , n (%)	129 (15)

RVOT, right ventricular outflow tract.

^aIt is of note that during high-pressure balloon dilation of RVOT and SCA, no data was recorded whether the high-pressure balloon was inflated to the predefined maximal diameter.

^bAdditional procedures during catheterization, e.g. balloon dilation or stenting of branch pulmonary arteries.

In the MELODY Registry, 109/845 (12.9%) patients had TPVI I.E.; of those, 68/109 (62%) were classified as definite and 41/109 (38%) as possible TPVI I.E. according to modified Duke criteria. In 100/109 (92%) patients, TPVI I.E. was blood-culture positive, whilst in 9/109 (8%) patients, TPVI I.E. was blood-culture negative. In the majority of patients with blood-culture positive TPVI I.E., Staphylococcal species were found ($n = 46/100$, 46%; [Supplementary material online, Table S5](#)).

Details on the primary management of TPVI I.E. and secondary outcomes are displayed in [Supplementary material online, Figure S5](#). Primary management of TPVI I.E. included conservative management with medical therapy in 41/109 (38%) patients, reintervention and medical therapy in 15/109 (14%) patients, and reoperation with TPVI explantation and medical therapy in 53/109 (48%) patients. However, 9/109 (8%) patients died due to TPVI I.E. after conservative management ($n = 5$), reintervention ($n = 2$), and reoperation with TPVI explantation ($n = 2$), respectively.

The proportion of patients who underwent conservative therapy only was lower in patients with definite TPVI I.E. compared to those

with possible TPVI I.E. according to modified Duke criteria ($n = 17/68$, 25% vs. $n = 19/41$, 46%; $P = 0.037$). Furthermore, the proportion of patients who presented with haemodynamic instability or septic syndrome was higher in patients with definite TPVI I.E. compared to those with possible TPVI I.E. ($n = 25/68$, 37% vs. $n = 3/41$, 7%; $P = 0.002$). Further information on the secondary outcomes in the subgroups of patients with possible and definite TPVI I.E. can be found in [Supplementary material online, Table S6](#).

In a multivariable Cox proportional hazard model ([Table 4](#)), one covariate showed a statistically significant association to the composite endpoint of TPVI I.E.: residual RV-to-PA pressure gradient (per 5 mmHg) (adjusted hazard ratio: 1.19, 95% CI 1.07–1.32; $P = 0.002$).

Secondary endpoints

Procedural complications

Details on procedural complications are summarized in [Table 5](#). Four patients (0.5%) died due to procedural complications (coronary

compression, $n = 3$; fatal bleeding, $n = 1$). All other patients survived until discharge. Surgical or interventional treatment of a procedural complication was necessary in 10 (1.2%) and in 17 patients (2.0%), respectively. In 50 patients (5.9%), procedural complications could be managed conservatively.

Invasive assessment of acute haemodynamic changes after transcatheter pulmonary valve implantation

Acutely, TPVI led to a significant reduction of the invasively measured peak RV-to-PA pressure gradient from 36 (IQR 24–47) to 12 (IQR 7–17) mmHg ($P < 0.001$). Subsequently, there was a significant reduction in the right ventricular systolic pressure from 61 (IQR 50–73) to 40 (IQR 34–49) mmHg and in the RV-to-systemic pressure ratio

from 0.64 (IQR 0.5–0.8) to 0.37 (IQR 0.3–0.5) ($P < 0.001$ for each). The PA diastolic pressure increased after TVPI from 10 (IQR 8–13) to 13 (IQR 10–16) mmHg ($P < 0.001$). The overall data on acute haemodynamic outcomes with invasive pressure measurement are displayed in Table 6.

Non-invasive follow-up assessment up to '1 year'

In a subset of patients, data on serial non-invasive follow-up assessment was available for review (Supplementary material online, Figure S4). There was sustained echocardiographic outcome at the '1 year' assessment when compared with early post-intervention (peak RVOT velocity: 2.58 ± 0.69 vs. 2.61 ± 0.64 m/s, $P = 0.001$; pulmonary regurgitation grade >2 : 1 vs. 1%; peak TR-jet velocity:

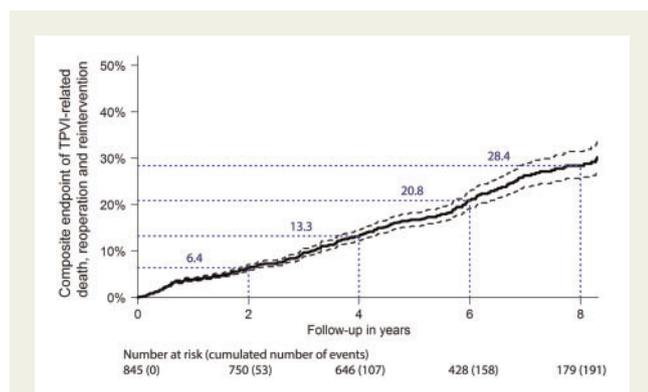


Figure 2 Cumulative incidence plots for the composite endpoint of transcatheter pulmonary valve implantation-related death, reoperation, and reintervention. At 6 years, the cumulative incidence of the composite endpoint was 20.8% (95% confidence interval 19.1–22.8), and at 8 years, the cumulative incidence of the composite endpoint was 28.4% (95% confidence interval 25.6–31.4).

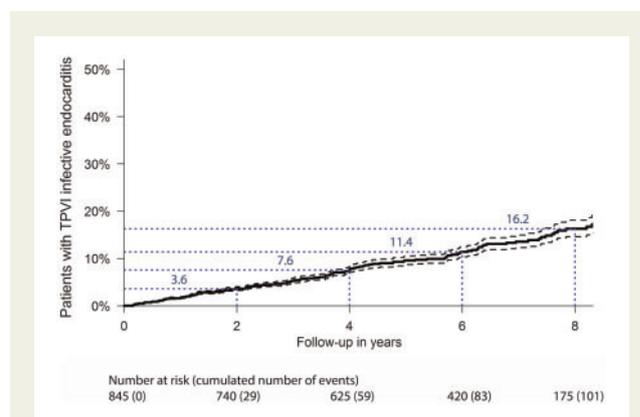


Figure 3 Cumulative incidence plots for transcatheter pulmonary valve implantation infective endocarditis. At 6 years, the cumulative incidence of transcatheter pulmonary valve implantation infective endocarditis was 11.4% (95% confidence interval 10.3–12.5), and at 8 years, the cumulative incidence of transcatheter pulmonary valve implantation infective endocarditis was 16.2% (95% confidence interval 14.6–18.1).

Table 3 Cox regression model related to the composite endpoint of TPVI-related death, reoperation, and reintervention

Variables	Coefficient	Standard error	Hazard ratio, exp (coefficient)	95% confidence interval		P-value
Calendar year of TPVI procedure ^a	-0.10	0.05	0.91	0.82	1.01	0.062
Patient age (years)	-0.04	0.01	0.96	0.95	0.98	0.0001
Patient gender: female (vs. male)	-0.40	0.16	0.67	0.49	0.93	0.015
Lesion: predominant PR (vs. predominant PS)	0.15	0.20	1.16	0.78	1.72	0.453
Lesion: mixed (vs. predominant PS)	-0.05	0.18	0.95	0.67	1.34	0.765
Prestenting: yes (vs. no)	-0.31	0.19	0.73	0.50	1.07	0.104
Size of delivery system: 20 mm (vs. 18 mm)	-0.29	0.20	0.75	0.51	1.10	0.141
Size of delivery system: 22 mm (vs. 18 mm)	-0.52	0.19	0.59	0.41	0.86	0.006
Residual RV-to-PA pressure gradient (per 5 mmHg)	0.19	0.04	1.21	1.12	1.30	<0.0001

Test for proportional hazard assumption: $P = 0.088$.

Test for goodness-of-fit: $P = 0.416$.

Significant differences in bold.

^a2006–2013.

Table 4 Cox regression model related to TPVI infective endocarditis

Variables	Coefficient	Standard error	Hazard ratio, exp (coefficient)	95% confidence interval		P-value
Calendar year of TPVI procedure ^a	0.09	0.07	1.10	0.96	1.26	0.183
Patient age (years)	-0.01	0.01	0.99	0.97	1.01	0.470
Patient gender: female (vs. male)	0.03	0.21	1.03	0.68	1.55	0.891
Lesion: predominant PR (vs. predominant PS)	0.20	0.26	1.22	0.73	2.04	0.455
Lesion: mixed (vs. predominant PS)	0.01	0.24	1.01	0.63	1.62	0.956
Prestenting: yes (vs. no)	0.00	0.30	1.00	0.55	1.82	0.994
Size of delivery system: 20 mm (vs. 18 mm)	-0.20	0.29	0.82	0.47	1.45	0.497
Size of delivery system: 22 mm (vs. 18 mm)	-0.27	0.27	0.76	0.45	1.29	0.312
Residual RV-to-PA pressure gradient (per 5 mmHg)	0.17	0.05	1.19	1.07	1.32	0.002

Significant differences in bold.

Test for proportional hazard assumption: $P = 0.189$.

Test for goodness-of-fit: $P = 0.597$.

^a2006–2013.

Table 5 Procedural complications

	Overall number n (% of n = 845; 95% CI)	Conservative management	Interventional treatment n (% of n = 845; 95% CI)	Surgical treatment	Death
Coronary compression	5 (0.6; 0.21–1.42)	0 (0; 0–0.55)	0 (0; 0–0.55)	2 (0.2; 0.01–0.92)	3 (0.4; 0.07–1.09)
Bleeding due to conduit rupture	7 (0.8; 0.36–1.74)	0 (0; 0–0.55)	6 (0.7; 0.29–1.58)	0 (0; 0–0.55)	1 (0.1; 0–0.74)
Bleeding due to pulmonary artery injury	5 (0.6; 0.21–1.42)	1 (0.1; 0–0.74)	3 (0.4; 0.07–1.09)	1 (0.1; 0–0.74)	0 (0; 0–0.55)
Pre-stent dislodgment	2 (0.2; 0.01–0.92)	1 (0.1; 0–0.74)	1 (0.1; 0–0.74)	0 (0; 0–0.55)	0 (0; 0–0.55)
TPVI dislodgment	3 (0.4; 0.07–1.09)	0 (0; 0–0.55)	1 (0.1; 0–0.74)	2 (0.2; 0.01–0.92)	0 (0; 0–0.55)
Obstruction of pulmonary artery branches	1 (0.1; 0–0.74)	0 (0; 0–0.55)	1 (0.1; 0–0.74)	0 (0; 0–0.55)	0 (0; 0–0.55)
Balloon rupture	13 (1.6; 0.87–2.64)	10 (1.2; 0.61–2.20)	3 (0.4; 0.07–1.09)	0 (0; 0–0.55)	0 (0; 0–0.55)
Vascular access complications	22 (2.6; 1.70–3.93)	18 (2.1; 1.33–3.37)	1 (0.1; 0–0.74)	3 (0.4; 0.07–1.09)	0 (0; 0–0.55)
Arrhythmia	15 (1.8; 1.05–2.93)	15 (1.8; 1.05–2.93)	0 (0; 0–0.55)	0 (0; 0–0.55)	0 (0; 0–0.55)
Other ^a	8 (0.9; 0.45–1.89)	5 (0.6; 0.21–1.42)	1 (0.1; 0–0.74)	2 (0.2; 0.01–0.92)	0 (0; 0–0.55)
Overall	81 (9.6; 7.77–11.77)	50 (5.9; 4.5–7.73)	17 (2.0; 1.24–3.22)	10 (1.2; 0.61–2.20)	4 (0.5; 0.14–1.26)

^aOther, e.g. dislocation of pacemaker/ICD-leads, injury of a right ventricular papillary muscle, pulmonary embolism, pulmonary oedema. The 95% confidence intervals (CIs) correspond to an Agresti–Coulil interval.

3.1 ± 0.7 vs. 3.0 ± 0.6 m/s, $P = 0.16$). Furthermore, the early improvement in NYHA class after TPVI was sustained at the ‘1 year’ assessment. TPVI stent fractures led to reoperation in 6/633 (1.0%) patients (Supplementary material online, Table S4).

Discussion

The objective of the post-approval MELODY Registry was to obtain multicentre registry data after TPVI with the MelodyTM valve in a large-scale cohort of CHD patients. Currently, approximately 350 patients undergo TPVI with the MelodyTM valve in Europe per year. The MELODY Registry included 845 patients from 42 cardiac centres and, thus, represents the largest post-approval cohort of patients after TPVI with the MelodyTM valve to date.

Composite endpoint

The composite endpoint of TPVI-related death, reoperation, and reintervention showed an incidence rate of 4.2% per person per year (95% CI 3.7–4.9). In a multivariable Cox proportional hazard model, there was a strong association between the composite endpoint and the residual invasively measured RV-to-PA pressure gradient (per 5 mmHg) at the time of TPVI (adjusted hazard ratio: 1.21, 95% CI 1.12–1.30; $P < 0.0001$). These data suggest that one potential factor to reduce the risk of the composite endpoint could be to reduce the residual RV-to-PA pressure gradient at the time of TPVI. However, further research is necessary to assess the potential benefit of reduced residual RV-to-PA pressure gradients during follow-up.

When arguing for targeted gradient reduction during TPVI, however, the risks of coronary compression and conduit rupture related

Table 6 Acute haemodynamic outcome in the overall cohort, invasive pressure measurements

Parameters	Pre	Post	Median difference from baseline		P-value
	Median (IQR) (n; % of n = 845)		Median (IQR) (n; % of n = 845)	95% CI	
RV systolic pressure (mmHg)	61 (50–73) (n = 826; 98%)	40 (34–49) (n = 789; 93%)	-19.5 (-30 to -10) (n = 778; 92%)	-21 -18	<0.001
PA systolic pressure (mmHg)	24 (20–30) (n = 825; 98%)	28 (23–34) (n = 781; 92%)	3 (-1 to 8) (n = 771; 91%)	3 4	<0.001
PA diastolic pressure (mmHg)	10 (8–13) (n = 816; 97%)	13 (10–16) (n = 678; 80%)	3 (0 to 5) (n = 666; 79%)	2 3	<0.001
RV-to-PA pressure gradient (mmHg)	36 (24–47) (n = 821; 97%)	12 (7–17) (n = 777; 92%)	-23 (-34 to -12) (n = 764; 90%)	-26 -23	<0.001
Systemic systolic pressure (mmHg)	94 (85–106) (n = 751; 89%)	108 (95–121) (n = 663; 78%)	11 (0 to 24) (n = 649; 77%)	9 11	<0.001
RV-to-systemic pressure ratio	0.64 (0.5–0.8) (n = 747; 88%)	0.37 (0.3–0.5) (n = 649; 77%)	-0.26 (-0.4 to -0.1) (n = 635; 75%)	-0.27 -0.25	<0.001

The 95% confidence intervals (CIs) correspond to bias-corrected and accelerated bootstrap intervals.

Significant differences in bold.

PA, pulmonary artery; RV, right ventricle.

to more forceful TPVI expansion need to be considered. In the MELODY Registry, 26% of the stents that were used for pre-stenting were covered CP-stents (Supplementary material online, Table S2). Furthermore, an increasing use of covered stents for pre-stenting is reported as an attempt to prevent from bleeding in case of conduit rupture during stent implantation. The increased use of covered pre-stents might have an influence on outcome parameters and needs to be evaluated in further studies.

Another variable that showed a statistically significant association with the composite endpoint on multivariable testing was the use of a 22-mm Ensemble™ delivery system (vs. 18-mm: adjusted hazard ratio: 0.59, 95% CI 0.41–0.86; $P=0.006$). It could be hypothesized that in the MELODY Registry, 22-mm Ensemble™ delivery systems were chosen more often in patients with—in relative terms—smaller conduits, leading to a slight ‘overexpansion’ of the RV-to-PA conduits (Supplementary material online, Figure S3). However, further research is required to assess the potential benefits of this approach.

Transcatheter pulmonary valve implantation infective endocarditis

Transcatheter pulmonary valve implantation I.E. showed an incidence rate of 2.3% per person per year (95% CI 1.9–2.8). This data are comparable to a previous study with pooled data from 311 patients that showed an annualized I.E. rate of 2.4% after TPVI with the Melody™ valve.¹² The clinical impact of TPVI I.E. was substantial in the MELODY Registry since it was associated with significant morbidity and nine follow-up deaths. In the MELODY Registry, 68/109 (62%) patients were classified as definite and 41/109 (38%) as possible TPVI I.E. according to modified Duke criteria.^{11–14} Although in the MELODY Registry, patients with possible TPVI I.E. seemed to present with less severe disease compared with those who were classified as

definite TPVI I.E., the clinical utility of the modified Duke criteria related to the diagnostic classification and prognostication of TPVI I.E. remains to be determined. In particular, there are known limitations related to the visualization of the Melody valve™ due to artefacts of the stent frame,^{11,12} which might impact on the sensitivity and specificity of one of the major modified Duke criteria (i.e. ‘imaging positive for I.E.’). Thus, a revised clinical classification system for TPVI I.E. and longer follow-up might be useful to study this clinically relevant follow-up complication.

In the majority of patients with blood-culture positive TPVI I.E., Staphylococcal species were found ($n=46/100$, 46%). Transcatheter pulmonary valve implantation I.E. with Staphylococcal species led to 7/9 (78%) of deaths that were attributed to TPVI I.E. These findings are similar to previous findings that were obtained in an analysis of 76 unique published cases of endocarditis after TPVI with the Melody™ valve [Staphylococcal species: found in 47% cases, led to 8/9 (89%) deaths attributed to TPVI I.E.].¹⁴

The findings of a multivariable Cox proportional hazard model suggest that one potential factor to reduce the risk of developing TPVI I.E. could be to reduce the residual RV-to-PA pressure gradient at the time of TPVI. However, further research is necessary to assess the potential benefit of reduced residual RV-to-PA pressure gradients. Because there is only limited knowledge about specific risk factors (e.g. discontinuation of antiplatelet therapy during follow-up) for the development of I.E. after TPVI¹¹ as yet, patients should be strongly encouraged to apply general measures of endocarditis prevention (e.g. good dental hygiene). Furthermore, patients and medical personnel should be made aware of early signs of I.E. to allow for immediate treatment.

Procedural complications

Overall, major procedural complications (death, surgical, or interventional treatment required) occurred in 4.2% in the

MELODY Registry, which is comparable to previous studies including the expanded FDA Melody™ valve trial.^{3,8} Coronary compression after TPVI^{19,20} occurred in five patients (0.6%) leading to procedure-related death in three patients (0.35%) and emergency surgery in two patients (0.25%). Importantly, three patients after previous Ross-procedure suffered from coronary compression; these patients are already known to have a high risk for this major complication after TPVI.²⁰ Although the risk of coronary compression can be evaluated by thorough assessment prior to TPVI, it cannot be avoided completely. When high-pressure pre-dilation of the intended implantation site is performed, there is a risk of conduit rupture that needs to be considered. In the MELODY Registry, the incidence of fatal conduit rupture ($n = 1$, 0.1%) was lower than the risk of fatal coronary compression ($n = 3$, 0.35%).

Haemodynamic outcome

Acutely, TPVI with the Melody™ valve led to a significant reduction of the RV-to-PA pressure gradient and to a complete restoration of pulmonary valve function. These haemodynamic outcomes were sustained at '1 year' assessment, which is in line with previous studies^{3,8,21,22} confirming the haemodynamic efficacy of TPVI with the Melody™ valve.

Limitations

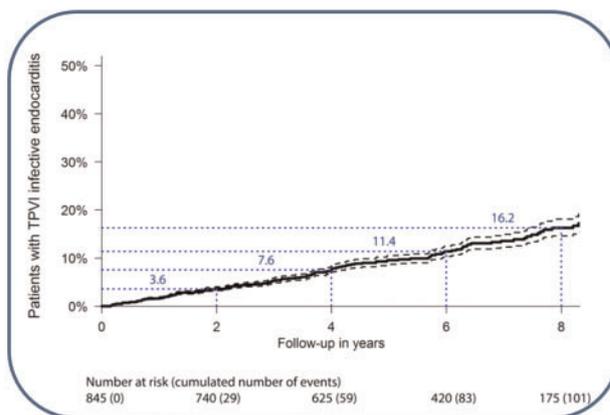
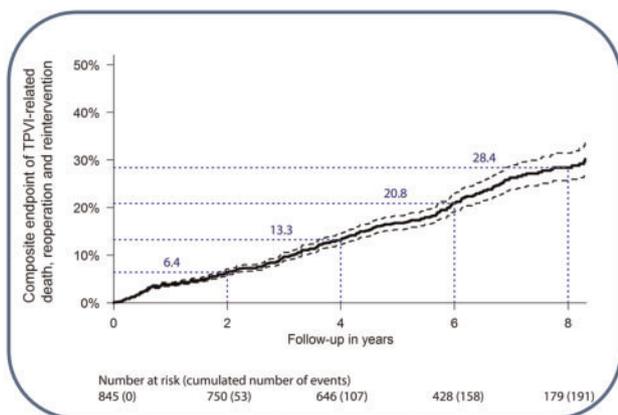
The most important limitations are the retrospective nature of the registry with self-reporting of data; furthermore, there was no auditing of data. Although the completeness of data on the primary endpoint parameters (i.e. composite endpoint and TPVI I.E.) was 100%, there was limited completeness of data on the secondary endpoint parameters, particularly for the non-invasive follow-up assessment.

Conclusions

The post-approval MELODY Registry confirms the efficacy of TPVI with the Melody™ valve in a large-scale cohort of CHD patients. The composite endpoint of TPVI-related death, reoperation, and reintervention showed an incidence rate of 4.2% per person per year (95% CI 3.7–4.9). The residual invasively measured RV-to-PA pressure gradient may serve as a target for further improvement in the composite endpoint and TPVI I.E. (*Take home figure*). However, TPVI I.E. remains a concern; TPVI I.E. showed an incidence rate of 2.3% per person per year (95% CI 1.9–2.8) and resulted in significant morbidity and mortality; therefore, patients should be strongly encouraged to apply general measures of endocarditis prevention (e.g. good dental hygiene). Furthermore, patients and medical personnel should be made aware of early signs of I.E. to allow for immediate treatment.

Multicenter registry of transcatheter pulmonary valve implantation (TPVI) with the Melody valve™:

- 845 patients included; median of 5.9 years of follow-up (range 0–11 years)
- A composite endpoint of TPVI-related events during follow-up (i.e. death, reoperation or reintervention) showed an incidence rate of 4.2% per person per year (95% CI 3.7–4.9)
- TPVI infective endocarditis showed an incidence rate of 2.3% per person per year (95% CI 1.9–2.8)



Invasively measured residual RV-to-PA pressure gradient (per 5 mmHg):

- Associated with the risk of the composite endpoint (adjusted hazard ratio: 1.21, 95% CI 1.12–1.30; $P < 0.0001$)
- Associated with the risk of TPVI infective endocarditis (adjusted hazard ratio: 1.19, 95% CI 1.07–1.32; $P = 0.002$)
- May serve as a target for further improvement in the composite endpoint and TPVI infective endocarditis.

Take home figure Cumulative incidence plots for the composite endpoint of transcatheter pulmonary valve implantation (TPVI)-related death, reoperation, and reintervention, and, separately, TPVI infective endocarditis (I.E.). The invasively measured residual RV-to-PA pressure gradient (per 5 mmHg) is associated with the risk of both outcomes.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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