Early View

Original article

Upfront triple combination therapy in severe paediatric pulmonary arterial hypertension

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Running head: Upfront triple combination therapy in paediatric PAH

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Take home message:

Upfront triple combination therapy in severe paediatric PAH resulted in significant clinical, haemodynamic and echocardiographic improvement and favorable 1-, 2- and 3-year survival rates, albeit 47% of the children receiving a Potts shunt during follow-up

Abstract

Introduction: Treatment strategies in paediatric pulmonary arterial hypertension (PAH) have evolved over the last years, but survival is still poor. Recently, in adults with severe PAH, upfront triple combination therapy (uTCT) from diagnosis has been reported to show significant clinical improvement and excellent long-term outcome. This retrospective, observational study aimed to assess the efficacy of uTCT in paediatric PAH.

Methods: Children diagnosed with PAH between 2010 and 2019 and started with uTCT were included. World Health Organization Functional Class (WHO-FC), haemodynamics, echocardiography, six-minute walking distance, and serum level of N-terminal-Pro-Brain-Natriuretic-Peptide were assessed at baseline, after three and six months and at last available follow-up. Events were defined as death, lung transplantation or Potts shunt.

Results: Twenty-one children (median age 4.8 years (2.5-12.8), 57% females) were included. All children except one were in WHO-FC III or IV (28% and 67%, respectively). After three months, one child had died and one child had received a Potts shunt. The remaining 19 children showed clinical and echocardiographic improvement, which persisted at six months. Children with idiopathic and heritable PAH showed one-, two-, and three-year transplant-free survival estimates of 100%, 94%, and 87%, albeit 47% of them receiving a Potts shunt during follow-up.

Conclusions: Children with severe PAH, but not pulmonary veno-occlusive disease, improved significantly with uTCT and showed beneficial up to 3-year survival rates, albeit 47% of them receiving a Potts shunt during follow-up. The role of a Potts shunt in conjunction to uTCT in paediatric PAH needs to be further established.

Keywords: pulmonary arterial hypertension, children, treatment, outcome

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare and life-threatening disease with untreated a median survival below three years in adult patients and even less in children.[1–3] Treatment strategies have evolved over the last years and have been associated with improved outcomes. Currently, available drugs intervene in three different pathways: the endothelin, nitric oxide (NO) and prostacyclin pathway. Phosphodiesterase 5-inhibitors (PDE5i) inhibit the breakdown of cyclic guanosine monophosphate, which is part of the NO pathway, endothelin receptor antagonists (ERA) inhibit the effects of endothelin-1 and hereby antagonise vasoconstriction, inflammation and proliferation, while prostacyclin-analogues induce vasodilation, antiproliferation and inhibit platelet aggregation.[4]

Initially, patients were started on monotherapies using these drugs, but nowadays guidelines recommend initiation of combination therapies.[5–7] Various studies showed improvement of clinical symptoms and a reduced risk of clinical worsening in adult PAH-patients treated with various combinations of ERAs, PDE5is and prostanoids.[8–10] Children on ERA therapy receiving subsequent add-on sildenafil therapy showed improvement of World Health Organization Functional Class (WHO-FC) and six-minute walking distance (6MWD).[11] Also, observational data suggest that survival is better in children receiving combination therapy compared to those receiving monotherapy.[12]

Recently, two studies reported on upfront triple combination therapy (uTCT), meaning targeting the three pathways simultaneously directly from time of diagnosis, including parenteral prostanoid therapy, in selected adult patients with severe PAH. These studies showed that uTCT was associated with significant clinical and echocardiographic improvement and an excellent long-term outcome after a mean follow-up of 41 and 24 months reported by Sitbon et al. and D'Alto et al., respectively.[13,14] Also, uTCT induced reversed remodeling of the right ventricle (RV).[14]

This study aimed to assess the efficacy of uTCT in children with severe PAH.

METHODS

This retrospective observational study reports the experience from two expert centers for children with PAH in two different countries. In France the Hôpital Necker Enfants malades serves as French Referral Center for Paediatric PH. In the Netherlands the University Medical Center Groningen (UMCG) serves as the National Referral Center for Pulmonary Hypertension in Childhood, where all Dutch paediatric patients suspected for PAH are referred. Patients in both centers are diagnosed and prospectively followed according to a standardised protocol and enrolled in respective registries. Ethical approval for the ongoing registries was obtained from the Medical Ethics Review Board from respectively the Hôpital Necker Enfants malades (in accordance with the request of the MR004) and the UMCG (METc 2008.009). Written informed consent from the patients (and/or their guardians) is given at enrolment in the registry.

Patients

Children (≤18 years of age) with idiopathic or heritable PAH (IPAH/HPAH), PAH associated with congenital heart disease (PAH-CHD), or PAH associated with other conditions, referred between June 2010 and February 2019 to the French or Dutch Referral Center and started with uTCT were included. In all children PAH diagnosis was confirmed by right heart catheterisation (RHC) (mean pulmonary arterial pressure (mPAP) ≥25 mmHg, pulmonary vascular resistance index (PVRi) ≥3 Wood units.m^2, and mean pulmonary capillary wedge pressure ≤15 mmHg).[15] The current study cohort consists of those children, who were considered at highest risk according to the paediatric risk stratification tool, including WHO-FC III or IV, a reduced RV function, significantly elevated N-terminal-Pro-Brain-Natriuretic-Peptide (NT-proBNP) level, and a PVRi >20 WU.m^2.[5,15]

Therapy

For this study uTCT was defined as the initiation of a PDE5i, an ERA, and prostanoids (subcutaneous [s.c.] or intravenous [i.v.]) within six weeks after diagnosis.

Clinical assessment

Clinical assessment took place at diagnosis/start of therapy (baseline), after three and six months, and at the last available follow-up. Clinical signs of RV failure (including hepatomegaly, peripheral edema, anorexia, nausea, fatigue, dyspnea), WHO-FC, echocardiography, 6MWD, and NT-proBNP level were assessed. Systolic RV function was assessed by echocardiography and included qualitative assessment by eyeballing (good/moderate/poor), and quantitative assessment using tricuspid annular plane systolic excursion (TAPSE). Invasive haemodynamics were assessed at baseline. Follow-up catheterisations were done at discretion of the treating physician.

Statistics

Data are presented as median (interquartile range [IQR]) or frequencies (percentage). Differences in clinical parameters at baseline and follow-up were analysed using Wilcoxon signed rank test or McNemar test.

Survival was defined as no death (lung transplantation [LTx] as censored event), transplant-free survival as no death or LTx and event-free survival as no death, LTx or Potts shunt. Differences in characteristics between patients with and without an event were compared using Mann-Whitney U test, Chi-squared test or Fisher's exact test.

Cox proportional hazard analysis and time-dependent Cox regression analysis were used to test the predictive value for (transplant-free/event-free) survival of the parameters assessed at baseline, at three months and the change between baseline and three months. Kaplan-Meier method was used to estimate (transplant-free/event-free) survival with the date of diagnostic RHC as the start point with truncating at 36 months because of low number of patients thereafter and for comparing with adult studies.[13,14] A p-value <0.05 was considered statistically significant.

RESULTS

Between June 2010 and February 2019 in the two participating centers 21 children were initiated with uTCT. Nineteen children were diagnosed either IPAH or HPAH, whereas two children had PAH-CHD (one child with PAH-CHD and coincidental shunt (atrial septal defect) with a *SOX17* mutation and one child with PAH-CHD after neonatal arterial switch operation for simple transposition of the great arteries (respectively PAH-CHD group 3 and 4 according to the most recent clinical classification of pulmonary hypertension (PH)).[5,16,17]

In two children, initially diagnosed as IPAH, the diagnosis was eventually changed into pulmonary veno-occlusive disease (PVOD) by histopathological examination of lung tissue collected either post-mortem or at LTx (respectively 0.7 months and 10.6 months after start of uTCT).

Seven children were diagnosed HPAH (*BMPR2* mutation n=5 and *TBX4* variant n=2), and one child had PAH associated with a Von Hippel-Lindau gene mutation (included in the IPAH/HPAH-population).[18] Median age at time of diagnosis was 4.8 years (2.5-12.8) with a slight dominance of females (57%). All children except one were in WHO-FC III or IV (28% and 67% respectively). Baseline clinical, echocardiographic and haemodynamic characteristics are shown in Tables 1 and 2, respectively. Poor systolic RV function was present in 86% of the children and TAPSE was clearly decreased. Pericardial effusion (PE) was present in 33%. Haemodynamic evaluation at baseline was performed between 15 days before and 19 days after baseline.

Treatment

The median time between initiation of the first and third PAH-targeted therapy was 0.2 months (0.0-0.4). All children received sildenafil (10 mg and 20 mg t.i.d. for children with a body weight below and above 20 kg, respectively) and bosentan (2 mg/kg b.i.d.).[19,20] Ten children received i.v. epoprostenol (maximum dose 20-33 ng/kg/min) and 11 children s.c. treprostinil (maximum dose 22-50 ng/kg/min).

In nine children uTCT was initiated at the paediatric intensive care unit (PICU) either because of clinical condition at presentation or because of institutional policy to initiate parenteral vasoactive agents in a PICU setting. Supportive therapy at time of initiation of uTCT included: inotropic support (10%), diuretics (29%), anticoagulation (19%), or oxygen suppletion (33%). None of the children received ventilatory support.

Assessments of treatment effect

Between the start of uTCT and three months follow-up assessment one patient died 0.7 months after start of uTCT, with a revised post-mortem diagnosis of PVOD. One IPAH-patient received a Potts shunt after 0.8 months since start of uTCT.

At three months follow-up (IQR 2.8-3.6), 17 out of the remaining 19 children had improved to WHO-FC I or II, whereas two IPAH/HPAH-patients improved to WHO-FC III. Clinical RV failure, present in nearly 30% of the children before start of uTCT, had recovered in all. Echocardiographic evaluation of RV function, judged poor at baseline in 16 out of 19 children, had recovered in all but one, also reflected by significant improvement of TAPSE. The one child in who RV function did not improve was diagnosed with PVOD 10.6 months after start of uTCT. NT-proBNP had decreased in 15 of 19 children and 6MWD, available in ten children, improved significantly (Table 3). Between three and six months follow-up no further patients died. The improvements observed at three months follow-up persisted at six months follow-up.

In ten patients, a follow-up RHC was performed at discretion of the treating physician after a median follow-up of 6.8 months (IQR 5.5-7.2). Median mPAP had decreased from 72 mmHg (62-99) to 48 mmHg (40-70), median PVRi from 18.6 $WU.m^2$ (13.8-22.5) to 9.2 $WU.m^2$ (5.8-14.5), whereas median cardiac index (CI) had increased from 4.3 l/min/m^2 (3.2-4.4) to 5.1 l/min/m^2 (3.9-5.5) and median systemic venous oxygen saturation (SvO_2) from 63% (57-70) to 71% (69-75)(all comparisons $p<0.05$).

Outcome

Median follow-up of the total study cohort of 21 children was 2.5 years (1.1-6.3).

Two children (eventually diagnosed PVOD) reached an endpoint within one year after initiation of uTCT (one death, one LTx). Two children with PAH-CHD survived without events with a follow-up of 0.3 and 1.1 years respectively.

Of the 17 children with IPAH/HPAH, two children underwent LTx 2.4 and 4.1 years after start of uTCT (one *BMPR2* mutation carrier and one IPAH-patient, respectively). Two children with IPAH/HPAH died: one *BMPR2* mutation carrier died one day after undergoing percutaneous Potts procedure (13.1 months after start of uTCT); the other child (IPAH) died 4.4 years after a Potts procedure (6.3 years after start of uTCT), not PAH-associated but due to cachexia associated with anorexia nervosa. In total, eight children with IPAH/HPAH underwent a Potts shunt during follow-up. The timeline of events is shown in Figure 1.

Indications for Potts shunt consisted of clinical worsening (CW)(n=5), lack of improvement (n=2), or recurrent line infections under i.v. epoprostenol therapy (n=1). CW was defined as recurrent syncope, worsening of WHO-FC, RV function deterioration, and/or increasing NT-proBNP level during follow-up. Lack of improvement was defined as sustained high WHO-FC (III or IV), sustained poor RV function and/or sustained high NT-proBNP level.

One-, two- and three-year survival rates and transplant-free survival rates in all patients were 95%, 90% and 90%, and 90%, 85%, and 78%, respectively (Figure 2A). Figure 2B displays the Kaplan Meier curves of the transplant-free survival stratified for type of PAH.

Children with IPAH/HPAH on uTCT had one-, two- and three-year survival rates of 100%, 94% and 94%, respectively. One-, two- and three-year transplant-free survival rates were 100%, 94%, and 87%, respectively (Figure 3).These compare more favorable to transplant-free survival predicted by the paediatric risk stratification tool proposed at the World Symposium on Pulmonary Hypertension (WSPH)(67% and 42% for 1- and 3-year transplant-free survival rates, respectively).[15,21] Observed one-, two- and three-year event-free survival rates were 88%, 69% and 55%, respectively (Figure 3).

Children with an event more often carried a *BMPR2* mutation (p=0.045) and had lower SvO_2 at baseline RHC (p=0.025). Time-dependent Cox regression analysis did not identify any of the collected variables as predictor for survival, not at baseline nor after three months uTCT.

Clinical condition of survivors at last follow-up

Thirteen of 17 children with IPAH/HPAH survived without LTx during the study period. Six of these had received a Potts shunt during follow-up. Of the seven surviving children without a Potts shunt, five were still on uTCT (median) 2.5 years (IQR 2.0-3.3) after start of uTCT. In two children, s.c. treprostinil was stopped, either because of clinical and echocardiographic improvement (infantile *TBX4* mutation carrier) or because of parental will (IPAH). Both children continued on oral dual combination therapy and were in a good clinical condition at last available follow-up one month and 5.4 years after termination of prostanoids respectively. All children except one were in WHO-FC I or II, and median NT-proBNP level was 66 ng/L (46-236). None of the children had clinical signs of RV failure, and echocardiographic evaluation revealed a good systolic RV function with no PE in all seven children (Table 4).

Of the six surviving children with a Potts shunt, parenteral prostanoid therapy was stopped in five, while oral dual combination therapy was continued. In one child, uTCT with i.v. epoprostenol was weaned after the Potts shunt but then restarted within 14 months because of CW. All "Potts-children" were in WHO-FC I or II, had no clinical signs of RV failure, had a median NT-proBNP level of 70 ng/L (61-179), and echocardiography showed a good systolic RV function with no PE in all six children (Table 4).

DISCUSSION

This study shows that children with severe PAH, but not PVOD, improved significantly with uTCT. This improvement sustained up to one year in the majority of children. Transplant-free survival rates at one-, two- and three-years showed superior to predicted transplant-free survival estimates calculated using the WSPH paediatric risk stratification tool. However,

almost half of the children received a Potts shunt during follow-up. The role of a Potts shunt in conjunction to uTCT in paediatric PAH needs to be further established.

Current guidelines for the treatment of IPAH/HPAH recommend start of combination therapy instead of monotherapy in patients at high risk. Recently a more aggressive, alternative treatment strategy for these patients has been proposed. In two separate studies, Sitbon et al. and D'Alto et al. reported the use of uTCT in high-risk adult PAH-patients and showed dramatic improvements in clinical condition, haemodynamics and reversed remodeling of the RV.[14,15] After median follow-up periods of two and over three years respectively, uTCT, including either i.v. epoprostenol or s.c. treprostinil, resulted in an impressive 70% reduction in PVR, 30% reduction in mPAP and over 100% increase in CI. Sitbon reported one-, two- and three-years survival of 94%, 94% and 94%, respectively and D'Alto a two-years survival of 100%, both comparing substantially more favorable to predicted survival in these high-risk patients based on current era risk scores.[13,14] Survival in paediatric PAH is reported to be worse than in adults, with young age as independent risk factor. Nevertheless, the current pilot study shows that uTCT also in children with PAH at high risk resulted in significant clinical and echocardiographic improvement after three and six months. Clinical risk factors in these children, such as WHO-FC III/IV and PVRi >20 WU.m^2, were comparable to the adult population of Sitbon and D'Alto.[13,14] Both recruiting centers follow the most current algorithms for treatment of children with PAH, recommending the initiation of intravenous prostanoid therapy, either or not in combination with other PAH-targeted therapy, in high-risk children.[5,15] Although in this retrospective study no predefined criteria were used for initiating uTCT, all children (except one) were in WHO-FC III or IV with either RV dysfunction and/or seriously increased NT-proBNP values and/or PVRi >20 WU.m^2 (as shown in Table 1 and 2). Invasive haemodynamics, assessed in half of the children, showed a 50% reduction in PVRi, 30% reduction of mPAP and 20% increase in CI. Since in contrast to adults, CI is generally longtime preserved in children with severe PAH, the proportional smaller increase in CI in children compared to adults, may be explained by the rather preserved CI in children with

severe PAH.[22,23] With a median follow-up time of more than 2.5 years, observed one-, two-, and three-year transplant-free survival rates in children with IPAH/HPAH were 100%, 94%, and 87%, respectively, more favorable than one- and three-year transplant-free survival estimates of 67% and 42% predicted by the WSPH paediatric risk stratification tool.[15,21] However, in the current cohort eight out of 17 children with IPAH/HPAH underwent a Potts shunt during follow-up, resulting in one-, two- and three-year event-free survival rates of 88%, 69% and 55%, respectively. This observation suggests that from one year after start of uTCT a substantial number of the children with IPAH/HPAH were considered to need additional intervention, mainly due to CW or lack of improvement. The Potts shunt is a procedure that is performed selectively in children with IPAH/HPAH and the availability and access to the Potts shunt in the study centers may have biased this number of events. The exact role of the Potts shunt in conjunction to uTCT in this group of children with severe IPAH/HPAH needs to be further established. One patient died perioperatively after undergoing a Potts procedure, illustrating associated risks with this procedure and the need for proper patient selection. Follow-up of surviving children with and without a Potts shunt, revealed that patients in both groups were in good clinical condition at last follow-up, although follow-up time since diagnosis was substantial longer in those who underwent a Potts procedure, making direct comparisons hazardous. Parenteral prostanoid therapy was stopped in five out of six children with a Potts shunt versus two out of seven children without Potts shunt. Whether the good clinical condition of the patients without a Potts shunt will last until similar follow-up time of the Potts-patients, or whether the Potts-patients have persisted in good clinical condition due to or despite the Potts shunt, cannot be answered by the current study.[24–26]

None of the collected variables were identified as predictor for survival, not at baseline nor after three months uTCT. The selected high-risk status of the children in this cohort, with high WHO-FC, high PVRi, poor systolic RV function and high NT-pro-BNP, may explain why the established prognostic value of these factors in paediatric PAH, were not predictive for outcome within this high-risk cohort. The current study clearly illustrates that uTCT including

parenteral prostanoids, is not an appropriate therapy in children with POVD, with both children with PVOD having an event (death or LTx) within the first year after diagnosis. It does also underscore that the differentiation between IPAH and PVOD at diagnosis may be difficult. The collection of lung tissue at time of diagnosis for confirmation of the diagnosis PVOD is not advised due to the high risks of lung biopsy in these patients, while CT-diagnosis may be ambiguous. Adverse response to vasodilating therapy is one of the diagnostic features of PVOD,[27] however, one of the PVOD-patients in the current study showed both clinical and echocardiographic (TAPSE) improvement with uTCT at three and six months. The rapid clinical deterioration of the children with PVOD underscores the need for early, proper diagnosis and every means should be used to accelerate this, including genetic testing to help refine treatment.[28]

Limitations

The current study is a retrospective observational study in a small number of selected patients accompanied by associated limitations. To demonstrate superiority of uTCT above other treatment strategies, for instance upfront double combination therapy, direct comparisons in a randomised controlled trial (RCT) would be required. However, conventional drug RCTs in paediatric PAH have been proven extremely challenging and therefore it is highly unlikely that such a trial will be performed any time soon. In the absence of RCTs, therefore the current observational data are instrumental in designing optimal treatment strategies for children with PAH. These current findings suggest excellent long-term effects of uTCT in children with severe PAH, with sustained effect in a substantial proportion of children.

Conclusion

This study provides preliminary evidence that in children with severe PAH uTCT is associated with substantial improvement in clinical condition, haemodynamics and RV function, and with favorable transplant-free survival during three year follow-up.

Nevertheless, during follow-up almost half of the children with IPAH/HPAH underwent a Potts procedure. The role of the Potts shunt in conjunction to uTCT in paediatric PAH needs to be further established.

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FIGURE LEGENDS

Figure 1. Timeline of all patients included in the study and the number of death, lung transplantation and Potts shunt.

* Patients undergoing a Potts shunt continued in follow-up. A Potts shunt is defined as an event in all event-free analyses.

LTx: lung transplantation.

Figure 2. A: Survival, transplant-free and event-free survival (no death, lung transplantation and Potts shunt) in all patients and **B.** Transplant-free survival stratified for diagnosis. Follow-up was truncated at 36 months.

PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; HPAH: heritable PAH; PVOD: pulmonary veno-occlusive disease; CHD: congenital heart disease; LTx: lung transplantation.

Figure 3. Survival, transplant-free and event-free survival (no death, lung transplantation and Potts shunt) in children with IPAH/HPAH started on upfront triple combination therapy. Follow-up was truncated at 36 months.

IPAH: idiopathic PAH; HPAH: heritable PAH; LTx: lung transplantation.

TABLES

Table 1. Baseline clinical characteristics

	median (IQR), n (%)

Age at diagnosis, years	4.8 (2.5-12.8)
Sex, female	12 (57)
Type of PAH	
IPAH/HPAH*	19 (90)
PAH-CHD	2 (10)
WHO-FC	
I	0 (0)
II	1 (5)
III	6 (28)
IV	14 (67)
Clinical symptoms of right heart failure, yes	6 (30)
Systolic blood pressure, mmHg	91 (88-104)
Diastolic blood pressure, mmHg	56 (46-65)
6MWD	
m	286 (155-337)
z-score[+]	-5.5 (-7.7 to -3.9)
NT-proBNP, ng/L	1530 (277-3354)
NT-proBNP <300 ng/L	5 (24)

*BMPR2 mutation: n=5; TBX4 variant: n=2.

[+]6MWD was not performed in 11 children (52%) because of too young age.

PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; HPAH: heritable PAH;

CHD: congenital heart disease; WHO-FC: World Health Organization Functional Class;

BMPR2: Bone morphogenetic protein receptor type II; TBX4: T-Box factor 4; 6MWD:

six-minute walking distance; NT-proBNP: N-terminal-Pro-Brain-Natriuretic-Peptide.

Table 2. Baseline echocardiographic and haemodynamic characteristics

	n	median (IQR), n (%)
Echocardiographic characteristics		

TAPSE	21	
mm		15.0 (13.1-17.7)
z-score		-2.1 (-4.5-0.9)
Poor systolic RV function	21	18 (86)
TI Vmax, m/s	20	4.6 (4.5-5.0)
Pericardial effusion, yes	21	7 (33)

Haemodynamic characteristics

mPAP, mmHg	21	70 (62-86)
mPCWP, mmHg	21	10 (6-11)
mSAP, mmHg	21	62 (56-74)
mRAP, mmHg	21	8 (5-9)
PVRi, WU.m^2	20	17.3 (13.1-25.3)
SVRi, WU.m^2	8	19.1 (13.9-25.3)
CI, l/min/m^2	20	3.8 (2.7-4.3)
SvO$_2$, %	21	65 (52-72)

CI: cardiac index; mPAP: mean pulmonary arterial pressure; mPCWP: mean pulmonary capillary wedge pressure; mSAP: mean systemic arterial pressure; mRAP: mean right atrial pressure; PVRi: pulmonary vascular resistance index; SvO$_2$: systemic venous oxygen saturation; SVRi: systemic vascular resistance index; TAPSE: tricuspid annular plane systolic excursion; TI: tricuspid insufficiency; RV: right ventricle; Vmax: maximum velocity.

Table 3. Comparison of clinical and echocardiographic characteristics between baseline and

three months follow-up in 19 surviving patients

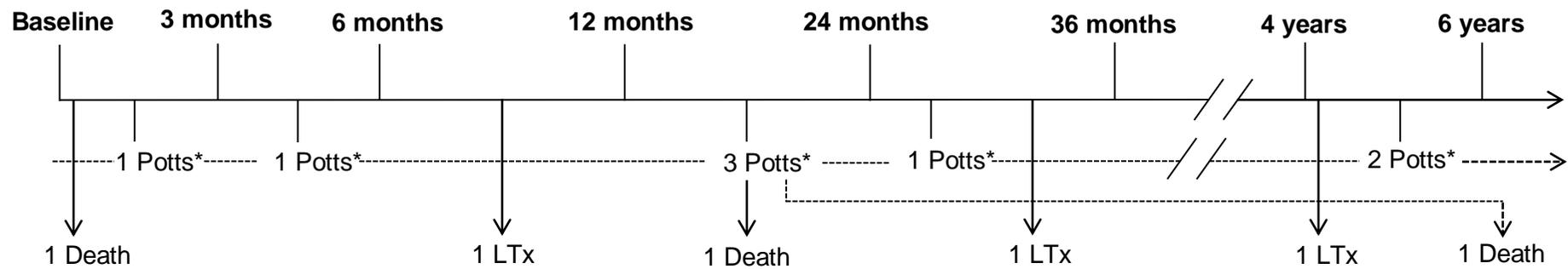|	At baseline n=19	At 3 months n=19	p-value
WHO-FC			**<0.001**
I	0 (0)	4 (21)	
II	1 (5)	13 (68)	
III	5 (26)	2 (11)	
IV	13 (68)	0 (0)	
Clinical symptoms of right heart failure, yes	5 (26)	0 (0)	0.063
Systolic blood pressure, mmHg	94 (88-105)	98 (94-108)	**0.037**
6MWD			
m	262 (143-342)	413 (372-488)	**0.008**
z-score	-5.6 (-7.9- -4.5)	-2.9 (-3.8 to -2.2)	**0.008**
NT-proBNP, ng/L	1530 (254-3580)	197 (66-433)	**0.001**
NT-proBNP <300 ng/L	5 (26)	13 (68)	**0.008**
TAPSE			
mm	14.0 (13.0-17.3)	19.2 (16.0-21.4)	**0.002**
z-score	-2.1 (-4.5- 0.7)	-0.2 (-1.7-1.4)	**0.004**
Poor systolic RV function	16 (84)	1 (5)	**<0.001**
TI Vmax, m/s	4.5 (4.5-5.0)	4.2 (3.3-4.5)	**0.004**
Pericardial effusion, yes	5 (26)	1 (5)	0.219

Data are presented as median (IQR) or number (%). NT-proBNP: N-terminal-Pro-Brain-Natriuretic-Peptide; RV:

right ventricle; TAPSE: tricuspid annular plane systolic excursion; TI: tricuspid insufficiency; Vmax: maximum

velocity; WHO-FC: World Health Organization Functional Class; 6MWD: six-minute walking distance.

Table 4. Outcome in children with IPAH/HPAH

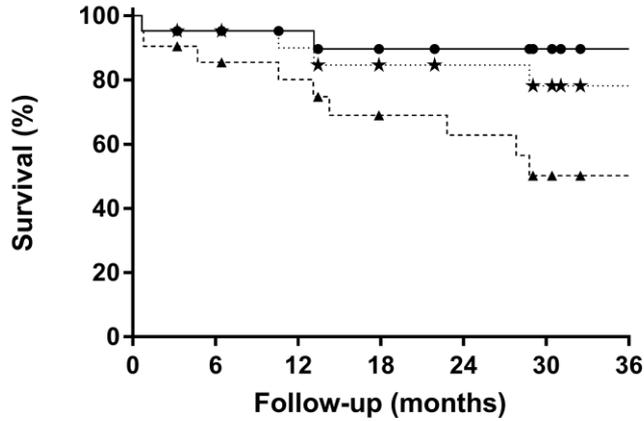|	Potts shunt N=8	No Potts shunt N=9
Death (all cause) / LTx	2 / 0	0 / 2
	Survivors	
	N=6	N=7
Median follow-up (years)		
Since initiation of upfront triple combination therapy	7.3 (2.4-8.3)	2.5 (1.5-4.0)
Since Potts procedure	2.6 (0.5-7.0)	NA
Prostanoids stopped, n	5 (83)	2 (29)
WHO-FC I/II	6 (100)	6 (86)
Clinical symptoms of right heart failure, yes	0	0
NT-proBNP (ng/L)	70 (61-179)	66 (46-236)
NT-proBNP <300 ng/L	5 (83)	6 (86)
Poor systolic RV function	0	0
Pericardial effusion, yes	0	0

Data are presented as median (IQR) or number (%).

PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; HPAH: heritable PAH; NT-proBNP: N-terminal-Pro-Brain-Natriuretic-Peptide; LTx: lung transplantation; RV: right ventricle; WHO-FC: World Health Organization Functional Class.

Baseline   3 months   6 months   12 months   24 months   36 months   4 years   6 years

-------- 1 Potts*-------- 1 Potts*--- 3 Potts* --------- 1 Potts*----------------------- //---------------------------- 2 Potts* ----------→

1 Death   1 LTx   1 Death   1 LTx   1 LTx   1 Death

*Patients undergoing a Potts shunt continued in follow-up. A Potts shunt is defined as an event in all event-free analyses.

**A**   **Survival, transplant-free survival and event-free survival in all patients**

No. at risk							
Death	21	19	17	14	13	11	8
Death or LTx	21	19	17	14	13	11	8
Death, LTx or Potts shunt	21	17	15	11	10	7	5

B   **Transplant-free survival stratified for diagnosis**
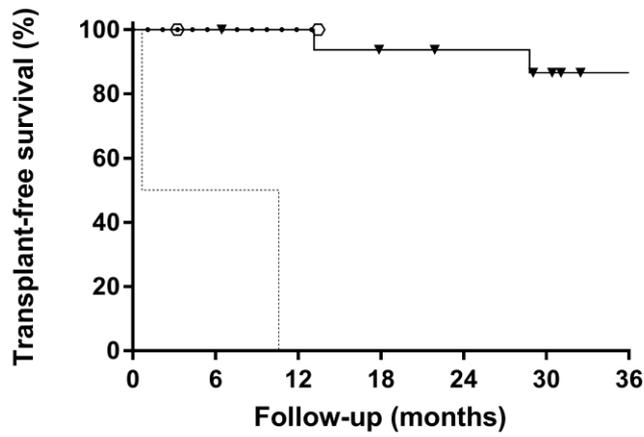
No. at risk							
IPAH/HPAH	17	17	16	14	13	11	8
PAH-CHD 3 and 4	2	1	0	0	0	0	0
PVOD	2	1	0	0	0	0	0

Survival, transplant-free survival and event-free survival in IPAH/HPAH
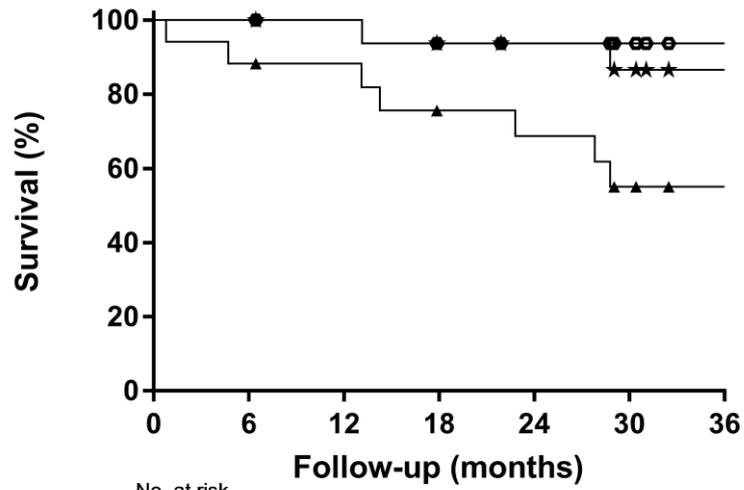
No. at risk

	Death						
Death	17	17	16	14	13	11	8
Death or LTx	17	17	16	14	13	11	8
Death, LTx or Potts shunt	17	15	14	11	10	7	5