

University of Groningen

## Parenteral Prostanoids in Pediatric Pulmonary Arterial Hypertension

Douwes, Johannes M; Zijlstra, Willemijn Mh; Rosenzweig, Erika B; Ploegstra, Mark-Jan; Krishnan, Usha S; Haarman, Meindina G; Roofthoof, Marcus T R; Postmus, Douwe; Hillege, Hans L; Ivy, D Dunbar

*Published in:*  
Annals of the American Thoracic Society

*DOI:*  
[10.1513/AnnalsATS.202012-1563OC](https://doi.org/10.1513/AnnalsATS.202012-1563OC)

**IMPORTANT NOTE:** You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2022

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Douwes, J. M., Zijlstra, W. M., Rosenzweig, E. B., Ploegstra, M.-J., Krishnan, U. S., Haarman, M. G., Roofthoof, M. T. R., Postmus, D., Hillege, H. L., Ivy, D. D., & Berger, R. M. F. (2022). Parenteral Prostanoids in Pediatric Pulmonary Arterial Hypertension: Start Early, Dose High, Combine. *Annals of the American Thoracic Society*, 19(2), 227-237. <https://doi.org/10.1513/AnnalsATS.202012-1563OC>

### Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

# Parenteral Prostanoids in Pediatric Pulmonary Arterial Hypertension Start Early, Dose High, Combine

Johannes M. Douwes<sup>1\*</sup>, Willemijn M. H. Zijlstra<sup>1\*</sup>, Erika B. Rosenzweig<sup>2</sup>, Mark-Jan Ploegstra<sup>1</sup>, Usha S. Krishnan<sup>2</sup>, Meindina G. Haarman<sup>1</sup>, Marcus T. R. Roofthoof<sup>1</sup>, Douwe Postmus<sup>3</sup>, Hans L. Hillege<sup>3</sup>, D. Dunbar Ivy<sup>4</sup>, and Rolf M. F. Berger<sup>1</sup>

<sup>1</sup>Center for Congenital Heart Diseases, Department of Pediatric Cardiology, Beatrix Children's Hospital, and <sup>3</sup>Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; <sup>2</sup>College of Physicians and Surgeons, Columbia University, New York, New York; and <sup>4</sup>University of Colorado, Children's Hospital Colorado, Aurora, Colorado

ORCID IDs: 0000-0003-3146-5831 (J.M.D.); 0000-0002-4385-5784 (R. M.F.B.).

## Abstract

**Rationale:** There are currently no data supporting specific dosing and weaning strategies for parenteral prostanoid therapy in children with pulmonary arterial hypertension (PAH).

**Objectives:** To describe the clinical practice of intravenous (IV) or subcutaneous (SC) prostanoid therapy in pediatric PAH and identify dosing strategies associated with favorable outcome.

**Methods:** From an international multicenter cohort of 275 children with PAH, 98 patients who received IV/SC prostanoid therapy were retrospectively analyzed.

**Results:** IV/SC prostanoids were given as monotherapy (20%) or combined with other PAH-targeted drugs as dual (46%) or triple therapy (34%). The median time-averaged dose was 37 ng/kg/min, ranging 2–136 ng/kg/min. During follow-up, IV/SC prostanoids were discontinued and transitioned to oral or inhaled PAH-targeted therapies in 29 patients. Time-dependent receiver operating characteristic analyses showed specific hemodynamic criteria at

discontinuation of IV/SC prostanoids (mean pulmonary arterial pressure < 35 mm Hg and/or pulmonary vascular resistance index < 4.4 Wood units [WU]·m<sup>2</sup>) identified children with favorable long-term outcome after IV/SC prostanoid discontinuation, compared with patients who do not meet those criteria ( $P = 0.027$ ). In the children who continued IV/SC prostanoids until the end of follow-up, higher dose (>25 ng/kg/min), early start after diagnosis, and combination with other PAH-targeted drugs were associated with better transplant-free survival.

**Conclusions:** Early initiation of IV/SC prostanoids, higher doses of IV/SC prostanoids, and combination with additional PAH-targeted therapy were associated with favorable outcome. Transition from IV/SC prostanoid therapy to oral or inhaled therapies is safe in the long term in selected children, identified by reaching hemodynamic criteria for durable IV/SC prostanoid discontinuation while on IV/SC prostanoid therapy.

**Keywords:** pulmonary hypertension; pediatrics; congenital heart disease; prostacyclin; outcome

(Received in original form December 21, 2020; accepted in final form June 28, 2021)

Ⓜ This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0. For commercial usage and reprints, please e-mail Diane Gern (dgern@thoracic.org).

\*These authors contributed equally to this work.

Supported by the Sebald Foundation, the Frederick and Margaret L. Weyerhaeuser Foundation, the Jayden de Luca Foundation, and National Institutes of Health (NIH)/National Center for Advancing Translational Sciences (NCATS) Colorado CTSA grant number UL1 TR002535.

**Author Contributions:** J.M.D. and W.M.H.Z.: design, data acquisition, analysis, interpretation, and drafting the work. E.B.R. and D.D.I.: design, data acquisition, interpretation, and drafting the work. M.-J.P., M.G.H., D.P., and H.L.H.: analysis, interpretation, and drafting the work. U.S.K.: interpretation and drafting the work. M.T.R.R.: data acquisition, interpretation, and drafting the work. R.M.F.B.: design, interpretation, and drafting the work. All authors: agreement with the final version of the manuscript.

Correspondence and requests for reprints should be addressed to Johannes M. Douwes, M.D., Ph.D., University Medical Center Groningen, Hanzplein 1, P.O. Box 30.001, 9700 RB Groningen, the Netherlands. E-mail: j.m.douwes@umcg.nl.

This article has a related editorial.

This article has an online supplement, which is available from this issue's table of contents at [www.atsjournals.org](http://www.atsjournals.org).

Ann Am Thorac Soc Vol 19, No 2, pp 227–237, Feb 2022

Copyright © 2022 by the American Thoracic Society

DOI: 10.1513/AnnalsATS.202012-1563OC

Internet address: [www.atsjournals.org](http://www.atsjournals.org)

Pulmonary arterial hypertension (PAH) is a rare, progressive pulmonary vascular disease eventually resulting in increased right ventricular afterload, right ventricular failure, and death (1). Despite the use of PAH-targeted drugs, survival of children with PAH remains unsatisfactory. Therefore, it is of utmost importance to evaluate and optimize current treatment strategies.

Before the year 2001, synthetic prostacyclin analogs, together referred to as prostanoids, were the only available PAH-targeted drugs and at that time required continuous intravenous (IV) administration. Subcutaneous (SC) administration of prostacyclin analogs has been available since 2002. Oral PAH-targeted drugs were introduced from 2001 onwards (2, 3). Current guidelines recommend starting oral PAH-targeted therapy in children with PAH at low risk, but to initiate IV/SC prostanoids without delay in patients with PAH at high risk, and furthermore, to escalate therapy to IV/SC prostanoids in those on oral therapies with inadequate clinical response (2, 3).

Currently, IV/SC prostanoids are not formally approved for children by the European Medicines Agency or United States Food and Drug Administration, but generally used as an accepted therapy in pediatric PAH. Also, although current guidelines provide recommendations of which patients should have IV/SC prostanoids initiated, optimal dosing remains arbitrary, as well as whether and when IV/SC prostanoids can be effectively transitioned to oral/inhaled PAH-targeted therapies (2, 3). Reported doses of IV/SC prostanoids used in pediatric PAH vary widely (4–7). Data regarding transition from IV/SC prostanoids to oral/inhaled therapies in pediatric PAH are scarce and lack long-term follow-up (8, 9).

We report clinical practice of IV/SC prostanoid therapy in three major referral centers for pediatric PAH, including time of initiation, dosing, and transition to oral and inhaled therapies, and we retrospectively investigated which treatment strategies were associated with favorable outcome.

## Methods

From an international cohort of pediatric patients with PAH, previously reported, all children who had received IV/SC prostanoids were selected (10). The original

cohort includes all consecutive pediatric patients with PAH seen in three major referral centers for pediatric pulmonary hypertension (PH) between 2000 and 2010: the Columbia University Medical Center, New York, New York; the Children's Hospital Colorado, Aurora, Colorado; and the Dutch National Referral Center for Pediatric PH, University Medical Center Groningen, the Netherlands. In this cohort, the diagnosis of PAH was confirmed during cardiac catheterization between the ages of 3 months and 18 years. PAH was defined as mean pulmonary artery pressure (mPAP) at least 25 mm Hg, mean pulmonary capillary wedge pressure  $\leq 15$  mm Hg, and indexed pulmonary vascular resistance (PVRi) at least 3 Wood units (WU)·m<sup>2</sup> (11). Children with a repaired shunt defect had PAH confirmed more than 1 year after corrective surgery. Children diagnosed with pulmonary veno-occlusive disease were excluded, as such children may show adverse response to IV/SC prostanoids (12, 13).

In all three centers, IV/SC prostanoid therapy was initiated according to the guidelines applicable at the time. These guidelines recommend IV/SC prostanoid initiation in patients at high risk for death or with insufficient response to nonparenteral therapy. In the absence of guidelines or generally accepted criteria for dosing, up-titration, and weaning of IV/SC prostanoids with or without transition to oral or inhaled therapies, such treatment decisions were made at distinction of the treating physician. Therefore, no predefined dosing strategies nor criteria for IV/SC prostanoid initiation or discontinuation were in place in this retrospective, multicenter, observational study.

The moment of IV/SC prostanoids initiation was defined as baseline to show the patient's characteristics, treatment characteristics, and outcome, starting from IV/SC prostanoid initiation, and to analyze the effect of IV/SC prostanoid treatment on outcome. Children were diagnosed according to the Updated Clinical Classification of PH, Nice, France, 2013, and grouped into idiopathic/heritable PAH (IPAH/HPAH), PAH associated with congenital heart disease (PAH-CHD) or associated PAH other than PAH-CHD (APAH-non-CHD) (14). Markers of disease severity, such as World Health Organization-functional class (WHO-FC), and hemodynamic measurements were collected

at baseline and at IV/SC prostanoid discontinuation.

The time between diagnosis and IV/SC prostanoid initiation and the duration of IV/SC prostanoid therapy were assessed. The proportion of follow-up time that patients were treated with IV/SC prostanoids is presented as the percentage of total follow-up time, calculated as (duration of IV/SC prostanoid therapy/total duration of follow-up)  $\times 100\%$ . To determine the IV/SC prostanoid dose that represents the dose over the therapy period and prevent confounding by (short-term) peak dosages, we assessed the time-averaged dose during the therapy period. According to literature as well as the treating physicians in the participating centers, treprostinil is dosed around 1.5–2.0 times higher than epoprostenol (15–17). Therefore, to make doses of treprostinil equipotent and thus comparable to doses of epoprostenol, doses of treprostinil were divided by 1.75.

Treatment intensity was defined as PAH-targeted monotherapy with IV/SC prostanoids if children used only IV/SC prostanoid during the study period, or as PAH-targeted dual or triple combination therapy if patients additionally received an endothelin receptor antagonist and/or a type-5 phosphodiesterase inhibitor for at least 3 months or until end of follow-up. We further determined whether IV/SC prostanoids were discontinued during the disease course and for what reasons.

## Statistical Analyses

Data are presented as number (percentage), mean (standard deviation) for normally distributed variables, or median (interquartile range [IQR]) for non-normally distributed variables, as appropriate. Independent samples *t* test, Kruskal-Wallis, Mann Whitney *U* test, and chi square and Fisher's exact test were used for between-group comparisons of baseline characteristics and treatment data. *P* values less than 0.05 were considered significant. Statistical analyses were performed using IBM SPSS Statistics 25 and RStudio 1.3.1056.

Outcome analyses were performed in children who received IV/SC prostanoids for at least 3 months, to allow for a relevant IV/SC prostanoid treatment duration. Overall transplantation-free survival was depicted from baseline (moment of IV/SC

prostanoids initiation), using a Kaplan-Meier curve. Patients were then grouped based on whether or not IV/SC prostanoid therapy was discontinued during follow-up.

For patients who discontinued IV/SC prostanoids during follow-up, endpoints included lung transplantation, death, and reinitiation of IV/SC prostanoid therapy. Children without an endpoint were censored at the last follow-up visit. In this patient group, transplant- and IV/SC prostanoid reinitiation-free survival was depicted from the moment of IV/SC prostanoid discontinuation. Time-dependent receiver operating characteristic (ROC) analyses were used to identify predictors and their cut-off values of durable prostanoid discontinuation (defined as favorable transplant and IV/SC prostanoid reinitiation-free survival) using RStudio with the TimeROC package (18). To selectively identify patients for whom prostanoid discontinuation proved durable, cut-off values were selected at a sensitivity of 100%.

For patients who continued IV/SC prostanoid therapy during follow-up, endpoints were defined as lung transplantation and death. For these patients, univariate Cox regression analysis was used to identify predictors for transplant-free survival. Multivariate Cox regression included all variables from univariate analysis. Time between diagnosis and

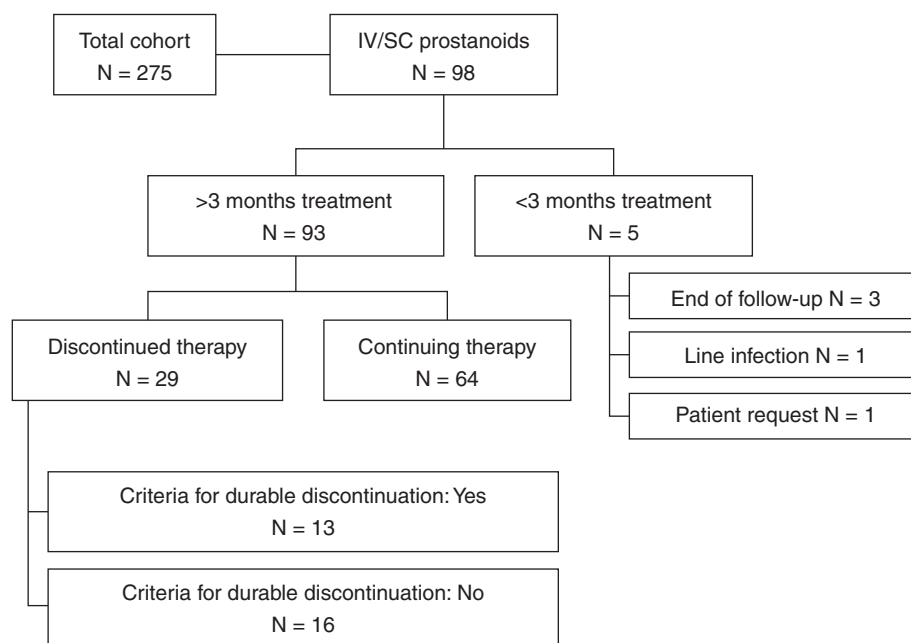
initiation of IV/SC prostanoid therapy has been included in the multivariate analysis to correct the analysis for any survival bias that could arise from choosing the moment of IV/SC prostanoid initiation as the baseline for survival analyses. Time-dependent ROC analyses were used to identify which prostanoid dose was associated with favorable transplant-free survival at 1, 3, and 5 years of follow-up, using RStudio with the TimeROC package (18). Cut-off values were selected based on the highest sum of sensitivity and specificity and used for Kaplan-Meier survival analyses. The latter analysis was truncated at 7 years of follow-up to reflect the follow-up period relevant to the ROC analyses.

## Results

From the original New York-Denver-Dutch cohort ( $n = 275$  children), 98 (36%) children received IV/SC prostanoids and were included in the current study (Figure 1). Patient and disease characteristics at baseline as well as treatment data are shown in Table 1. Compared with the original combined patient cohort, described previously, patients who received IV/SC prostanoids had more advanced disease, based on significantly higher WHO-FC, mPAP and PVRi (data not shown) (10).

For most children, IV/SC prostanoids were initiated within 1 year after diagnosis (Table 1). Sixty-eight patients used one type of IV/SC prostanoid, whereas 30 patients successively used more than one type of IV/SC prostanoid during their treatment period. The majority of children ( $n = 92$ , 94%) received IV epoprostenol, 28 children (29%) IV treprostinil, 10 children (10%) SC Treprostinil, and 1 child IV iloprost. Twenty children (20%) received IV/SC prostanoids as PAH-targeted monotherapy, 45 (46%) as dual combination therapy, and 33 (34%) as triple combination therapy. The median time-averaged dose during the therapy period was 37 ng/kg/min, ranging from 2 to 136 ng/kg/min.

Of the 98 patients who received IV/SC prostanoids, 5 received IV/SC prostanoids for less than 3 months within the study period. In three of these patients, the study period ended within 3 months after IV/SC prostanoids initiation. These patients were on continuing IV/SC prostanoid therapy at the end of the study period. The other two children were weaned off IV/SC prostanoids within 3 months after initiation, owing to severe line infections ( $n = 1$ ) or per patient wish ( $n = 1$ ). The latter child subsequently died owing to progressive right ventricular failure. These patients were excluded from outcome analyses, because outcome events may not



**Figure 1.** Patient inclusion and grouping. IV = intravenous; SC = subcutaneous.

**Table 1.** Patient and treatment characteristics of the study cohort

	All Patients (N = 98)		>3 Mo Prostanoid Treatment (N = 93)	
	N	Value	N	Value
Age diagnosis, yr	98	5.5 (2.6–11.6)	93	5.3 (2.6–11.5)
Female, n (%)	98	56 (57)	93	55 (59)
Diagnosis	98		93	
IPAH/HPAH		56 (57)		53 (57)
PAH-CHD		35 (36)		33 (36)
Hemodynamic relevant shunt		9		9
APAH-non-CHD		7 (7)		7 (8)
WHO-FC	84		80	
I		4 (5)		4 (5)
II		16 (19)		16 (20)
III		26 (31)		23 (29)
IV		38 (45)		37 (46)
mPAP, mm Hg	86	65 ± 19	82	65 ± 19
mRAP, mm Hg	85	7 ± 4	81	7 ± 4
PVRi, WU·m <sup>2</sup>	83	21.7 ± 14.4	79	21.5 ± 14.4
Cardiac index, L/min/m <sup>2</sup>	81	3.7 ± 2.1	77	3.8 ± 2.2
mPAP/mSAP	86	1.02 ± 0.31	82	1.02 ± 0.31
Qp/Qs	81	0.97 ± 0.18	77	0.98 ± 0.18
Prostanoid treatment:				
Time between diagnosis and IV/SC prostanoid initiation (months)	98	0.7 (0.0–8.5)	93	0.7 (0.0–8.5)
Start <1 yr after diagnosis	98	75 (77)	93	71 (86)
% of disease course on IV/SC therapy	98	82 (45–99)	93	82 (50–100)
Type of prostanoid*	98		93	
IV epoprostenol		92 (94)		88 (95)
IV treprostinil		28 (29)		27 (29)
SC treprostinil		10 (10)		10 (11)
IV iloprost		1 (1)		1 (1)
Time-averaged prostanoid dose, ng/kg/min	98	37 (19–63)	93	37 (20–63)
Treatment intensity:	98		93	
PAH-targeted monotherapy		20 (20)		18 (19)
PAH-targeted dual therapy		45 (46)		43 (46)
PAH-targeted triple therapy		33 (34)		32 (34)

*Definition of abbreviations:* APAH-non-CHD = associated pulmonary arterial hypertension other than congenital heart disease; IPAH/HPAH = idiopathic or heritable pulmonary arterial hypertension; IV = intravenous; mPAP = mean pulmonary artery pressure; mPAP/mSAP = mean pulmonary-to-systemic artery pressure ratio; mRAP = mean right atrial pressure; PAH = pulmonary arterial hypertension; PAH-CHD = pulmonary arterial hypertension associated with congenital heart disease; PVRi = pulmonary vascular resistance index; Qp/Qs = pulmonary to systemic flow ratio; SC = subcutaneous; WHO-FC = World Health Organization functional class; WU = Wood units.

Data presented as median (interquartile range), number (percentage), or mean ± standard deviation.

\*Several patients had more than one type of prostanoid during their disease course.

be attributable to their very short-term prostanoid therapy.

### Children on More Than 3 Months of Prostanoid Therapy

Of the 93 children who received IV/SC prostanoids for at least 3 months, 18 died and 7 underwent lung transplantation during a median follow-up of 4.2 (IQR 1.8–8.0) years (Figure 2). Sixty-four patients were on continuing IV/SC prostanoid therapy until the end of follow-up, whereas IV/SC prostanoids were discontinued in 29 patients (30%) (Figure 1). Age, diagnosis, sex, and disease characteristics at baseline did not differ between these groups, except for a lower mean right atrial pressure in the

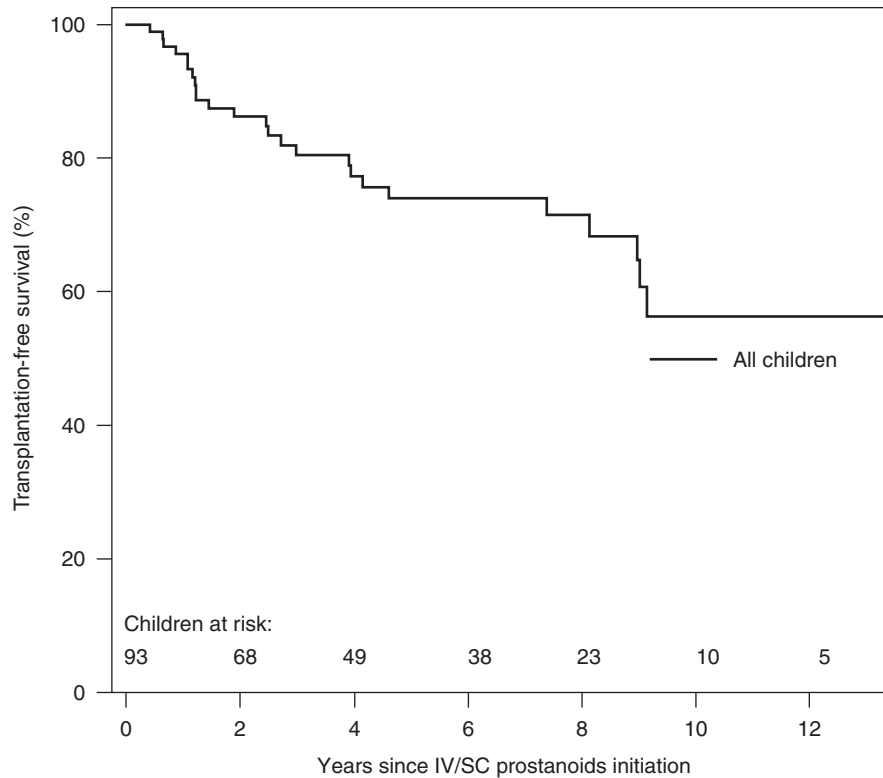
patients for whom IV/SC prostanoids were discontinued (Table 2). The children for whom IV/SC prostanoids were discontinued had started IV/SC prostanoids earlier in their disease course and had a lower mean dose during the therapy period (Table 2). Treatment intensity, i.e., PAH-targeted mono, dual, or triple therapy, did not differ between these two groups.

### Children Who Discontinued IV/SC Prostanoids Therapy

For 29 children, IV/SC prostanoids were discontinued during follow-up. These children were transitioned to oral and/or inhaled PAH-targeted therapies ( $n = 28$ ) or calcium channel blocker monotherapy

( $n = 1$ ). Reasons for discontinuation were being judged by the treating physician to do sufficiently well to discontinue IV/SC prostanoid therapy ( $n = 21$ ), IV/SC prostanoid side effects (weight loss, diarrhea,  $n = 1$ ) or IV-administration-related complications (line infection/sepsis,  $n = 3$ ), or patient wish or noncompliance ( $n = 4$ ). Children for whom IV/SC prostanoids were discontinued, as a group, had a relatively low WHO-FC (WHO-FC I  $n = 14$  [50%], II  $n = 12$  [43%], and III  $n = 2$  [7%]), mPAP ( $39 \pm 21$  mm Hg), and PVRi ( $11 \pm 15$  WU·m<sup>2</sup>) at the moment of IV/SC prostanoid discontinuation, which was significantly lower compared with their baseline values (WHO-FC  $P < 0.001$ , mPAP  $P < 0.001$ , and





**Figure 2.** Transplantation-free survival of children who received intravenous (IV)/subcutaneous (SC) prostanoids from IV/SC prostanoid initiation for all children treated with IV/SC prostanoids for at least 3 months during their disease course. One-, 3-, and 5-year survival rates were 94%, 81%, and 74% respectively.

PVRI  $P = 0.015$ ). Variation in these variables within this group, owing to the non-predefined weaning strategies in the participating centers, allowed for analysis of predictors for durable IV/SC prostanoid discontinuation.

After discontinuation of IV/SC prostanoids, one child died without restarting IV/SC prostanoids, and for four children IV/SC prostanoids were restarted because of clinical deterioration. Of these latter four children, one received lung transplantation and one died later during follow-up. Time-dependent ROC analyses at 5-year follow-up showed that at the time of discontinuation, criteria for durable IV/SC prostanoid discontinuation, determined by ROC analysis (mPAP < 35 mm Hg [sensitivity 100%, AUC 0.77] and/or PVRI < 4.4 WU·m<sup>2</sup> [sensitivity 100%, AUC 0.81]) selected 13 (45%) children with favorable outcome without reinitiation of IV/SC prostanoids. In contrast, WHO-FC did not allow for the identification of children with such favorable outcome. Children who did not reach the criteria for durable IV/SC prostanoid discontinuation ( $n = 16$ ) showed less favorable outcome after IV/SC

prostanoid discontinuation (Figure 3), whereas disease severity at baseline and treatment characteristics did not differ between those who reached versus did not reach the criteria for durable IV/SC prostanoid discontinuation (Table 3).

#### Outcome of Children Who Continued of IV/SC Prostanoids

For 64 children, IV/SC prostanoids were continued during the study period (median (IQR) follow-up time, 2.6 [1.3–6.6] years). In this patient group, 1-, 3-, and 5-year survival rates were 93%, 72%, and 64%, respectively. We performed Cox regression analysis to identify predictors of transplant-free survival for children on continuing IV/SC prostanoids therapy. In univariate analysis, older age at diagnosis and higher mPAP, mean right atrial pressure, PVRI and mean pulmonary-to-systemic artery pressure ratio were associated with worse transplant-free survival, whereas triple and dual combination therapy were associated with better transplant-free survival, compared with prostanoid monotherapy (Table 4). Furthermore, a higher time-averaged dose of IV/SC prostanoid was associated with better

outcome. In multivariate analyses, higher dose of IV/SC prostanoid (hazard ratio [HR], 0.36 [0.17–0.74] per 10 ng/kg/min dose increase,  $P = 0.006$ ), shorter time between diagnosis and initiation of IV/SC prostanoid therapy (HR, 1.10 [1.01–2.00] per month increase,  $P = 0.022$ ), and dual combination therapy versus monotherapy (HR, 0.04 [0.00–0.66]  $P = 0.025$ ) were independently associated with better outcome.

To illustrate which time-averaged IV/SC prostanoid dose was associated with better outcome at 1-, 3- and 5-year follow-up, cut-off values for time-averaged dose of IV/SC prostanoid were identified with time-dependent ROC analyses (Table 5). Cut-off values for prostanoid dose were 25, 54, and 75 ng/kg/min at 1-, 3-, and 5-year follow-up, respectively. There was a significant survival difference between patients grouped based on these cut-off values (Figure 4).

#### Discussion

In this current international multicenter cohort, 36% of the children with PAH received IV/SC prostanoids during the

**Table 2.** Baseline patient and treatment characteristics, continuing versus discontinued IV/SC prostanoids

	Continuing Treatment (N = 64)		Discontinued Treatment (N = 29)		P Value
	N	Value	N	Value	
Age diagnosis, yr	64	6.2 (3.0–11.6)	29	4.6 (1.7–9.7)	0.281
Female, n (%)	64	37 (58)	29	18 (62)	0.699
Diagnosis	64		29		0.705
IPAH/HPAH		36 (56)		17 (59)	
PAH-CHD		24 (38)		9 (31)	
APAH-non-CHD		4 (6)		3 (10)	
WHO-FC	54		26		0.886
I		1 (2)		3 (12)	
II		11 (20)		5 (19)	
III		19 (35)		4 (15)	
IV		23 (43)		14 (54)	
mPAP, mm Hg	55	66 ± 19	27	64 ± 19	0.706
mRAP, mm Hg	54	8 ± 4	27	6 ± 4	0.034
PVRI, WU·m <sup>2</sup>	53	21.3 ± 14.7	26	21.7 ± 13.8	0.908
Cardiac index, L/min/m <sup>2</sup>	52	3.9 ± 2.4	25	3.5 ± 1.5	0.438
mPAP/mSAP	55	1.03 ± 0.32	27	1.00 ± 0.29	0.673
Qp/Qs	52	0.99 ± 0.19	25	0.96 ± 0.17	0.517
Prostanoid treatment:					
Time between diagnosis and IV/SC prostanoid initiation, mo	64	1.5 (0.0–14.7)	29	0.4 (0.0–1.2)	0.044
Start <1 yr after diagnosis	64	45 (70)	29	26 (90)	0.042
% of disease course on IV/SC therapy	64	97 (67–100)	29	56 (32–77)	<0.001
Type of prostanoid*	64		29		
IV epoprostenol		62 (97)		26 (90)	
IV treprostinil		17 (27)		10 (34)	
SC treprostinil		6 (9)		4 (14)	
IV iloprost				1 (3)	
Time-averaged prostanoid dose, ng/kg/min	64	43 (24–66)	29	28 (16–47)	0.015
Treatment intensity:	64		29		0.935
PAH-targeted monotherapy		13 (20)		5 (17)	
PAH-targeted dual therapy		29 (45)		14 (48)	
PAH-targeted triple therapy		22 (34)		10 (35)	

*Definition of abbreviations:* APAH-non-CHD = associated pulmonary arterial hypertension other than congenital heart disease; IPAH/HPAH = idiopathic or heritable pulmonary arterial hypertension; IV = intravenous; mPAP = mean pulmonary artery pressure; mPAP/mSAP = mean pulmonary-to-systemic artery pressure ratio; mRAP = mean right atrial pressure; PAH = pulmonary arterial hypertension; PAH-CHD = pulmonary arterial hypertension associated with congenital heart disease; PVRI = pulmonary vascular resistance index; Qp/Qs = pulmonary to systemic flow ratio; SC = subcutaneous; WHO-FC = World Health Organization functional class; WU = Wood units.

Data presented as median (interquartile range), number (percentage) or mean ± standard deviation.

\*Multiple patients had more than 1 type of prostanoid during their disease course.

course of their disease (10). Children had severe PAH and frequently started with IV/SC prostanoids early after diagnosis. Five-year survival rate was 74%, which is in the lower range of the overall survival rates reported in pediatric PAH, but favorable for a selected subgroup of high-risk patients with advanced disease as included in the current study (10, 19–21).

In the centers participating in this study, different dosing strategies for IV/SC prostanoids were in place, resulting in a wide variation in doses of IV/SC prostanoids, similar to previous studies reporting on prostanoid use in children (4–7, 22, 23). This variation conforms to

current guidelines for both adult and pediatric patients that recommend wide ranges of optimum dosage of IV/SC prostanoids (in children 40 to >150 ng/kg/min for epoprostenol) (2, 3). However, data to support optimum dosage in children with PAH are lacking. The current study of children on IV/SC prostanoids observed that higher prostanoid dose was associated with better outcomes. Moreover, early initiation of IV/SC prostanoid therapy and combination with additional PAH-targeted drugs were associated with better prognosis. These associations were independent from patient characteristics

and disease severity at baseline, indicating that these associations hold regardless of age, sex, baseline disease severity, or the presence or absence of a cardiac shunt. The beneficial effect of early initiation of IV/SC prostanoids and the combination with other PAH-targeted drugs is in line with a recent study, showing favorable outcomes in children with severe PAH who received upfront triple combination therapy (24).

To illustrate which “higher” IV/SC prostanoids dose would be associated with improved outcome, we identified dose cut-off values at three relevant follow-up time points. Survival analyses based on

**Table 3.** Patient and treatment characteristics in those who meet versus do not meet the criteria for durable IV/SC prostanoid discontinuation

	Patients Who Meet the Criteria (N = 13)		Patients Who Do Not Meet the Criteria (N = 16)		P Value
	N	Value	N	Value	
Age diagnosis, yr	13	4.2 (0.8–9.1)	16	5.1 (2.1–13.6)	0.254
Female n (%)	13	7 (54)	16	11 (69)	0.411
Diagnosis	13		16		0.186
IPAH/HPAH		10 (77)		7 (44)	
PAH-CHD		2 (15)		7 (44)	
APAH-non-CHD		1 (8)		2 (13)	
At baseline:					
WHO-FC I / II / III / IV	11	1 (9) / 1 (9) / 3 (27) / 6 (54)	15	2 (13) / 4 (27) / 1 (7) / 8(53)	0.649
mPAP, mm Hg	11	64 ± 18	16	64 ± 20	0.886
mRAP, mm Hg	11	6 ± 4	16	6 ± 4	0.736
PVRi, WU·m <sup>2</sup>	11	24.1 ± 15.9	15	20.1 ± 12.4	0.471
Cardiac index, L/min/m <sup>2</sup>	11	3.3 ± 1.8	14	3.6 ± 1.3	0.693
mPAP/mSAP	11	1.08 ± 0.31	16	0.94 ± 0.26	0.217
Qp/Qs	11	0.96 ± 0.23	14	0.96 ± 0.11	0.921
At IV/SC prostanoid discontinuation:					
WHO-FC I / II / III / IV	13	9(69) / 4 (31) / 0 / 0	15	5 (33) / 8 (53) / 2 (13) / 0	0.044
mPAP, mm Hg	13	24 ± 5	12	56 ± 18	<0.001
PVRi, WU·m <sup>2</sup>	13	3.5 ± 2.0	10	20.4 ± 19.3	0.022
Prostanoid treatment:					
Time between diagnosis and IV/SC prostanoid initiation, mo	13	0.2 (0.0–0.9)	16	0.5 (0.0–2.0)	0.177
Start <1 yr after diagnosis	13	12 (92)	16	14 (88)	0.672
% of disease course on IV/SC therapy	13	45 (32–77)	16	60 (37–75)	0.826
Type of prostanoid*	13		16		
IV epoprostenol		12 (92)		14 (88)	
IV treprostinil		3 (23)		7 (44)	
SC treprostinil				4 (25)	
IV iloprost				1 (6)	
Time-averaged prostanoid dose (ng/kg/min)	13	28 (17–51)	16	29 (16–45)	0.861
Treatment intensity:	13		16		0.748
PAH-targeted monotherapy		3 (23)		2 (13)	
PAH-targeted dual therapy		6 (46)		8 (50)	
PAH-targeted triple therapy		4 (31)		6 (38)	

*Definition of abbreviations:* APAH-non-CHD = associated pulmonary arterial hypertension other than congenital heart disease; IPAH/HPAH = idiopathic or heritable pulmonary arterial hypertension; IV = intravenous; mPAP = mean pulmonary artery pressure; mPAP/mSAP = mean pulmonary-to-systemic artery pressure ratio; mRAP = mean right atrial pressure; PAH = pulmonary arterial hypertension; PAH-CHD = pulmonary arterial hypertension associated with congenital heart disease; PVRi = pulmonary vascular resistance index; Qp/Qs = pulmonary to systemic flow ratio; SC = subcutaneous; WHO-FC = World Health Organization functional class; WU = Wood units.

Data presented as median (interquartile range), number (percentage) or mean ± standard deviation. Criteria for durable IV/SC prostanoid discontinuation defined as mPAP < 35 mm Hg or PVRi < 4.4 WU·m<sup>2</sup>, by time-dependent receiver operating characteristic analysis.

\*Multiple patients had more than 1 type of prostanoid during their disease course.

these cut-off values suggest that IV/SC prostanoid dose should be at least 25 ng/kg/min. Moreover, it shows that higher doses were associated with better outcome, whereas no ceiling effect could be demonstrated. This would suggest that

the higher the prostanoid dose, the better long-term outcome, independent of other risk factors or additional therapies.

High doses of IV/SC prostanoids should be given with caution, as high doses of IV/SC prostanoids have been reported to hold a risk

for high output failure (25). From a recent retrospective study in children with PAH treated with prostanoids, the authors suggested that doses higher than 60 ng/kg/min for epoprostenol or 100 ng/kg/min for treprostinil did not lead to further reduction



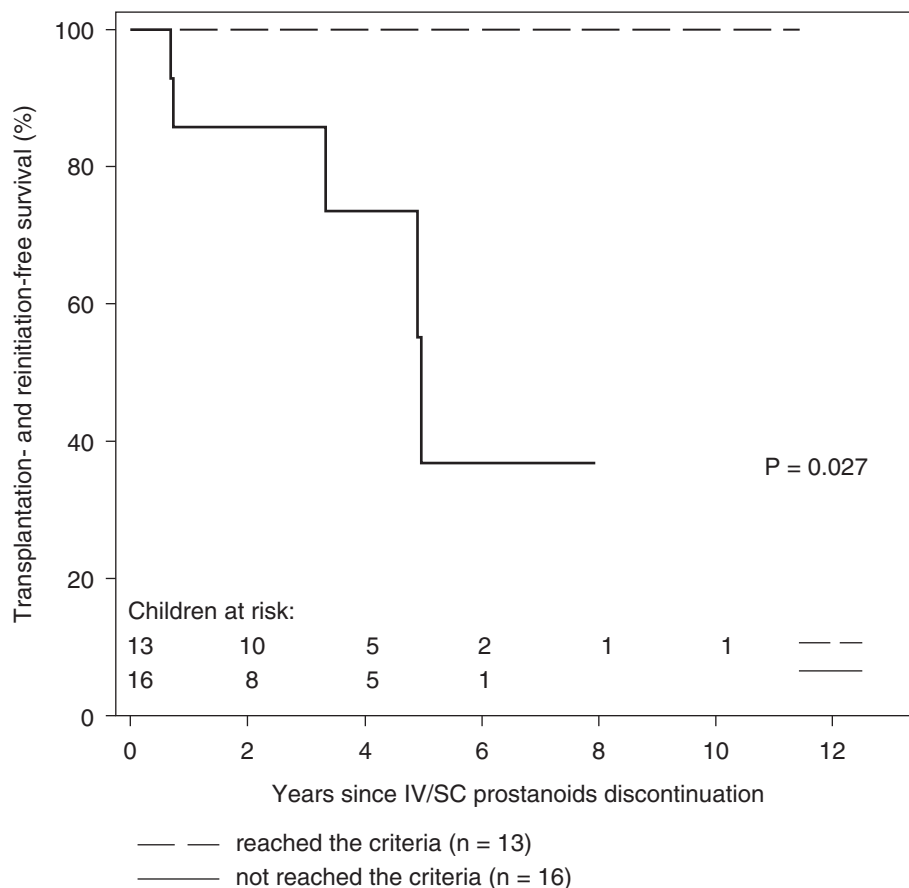
of mPAP (26). Our findings, however, suggest that there may be improved outcomes beyond hemodynamics with higher dosing. However, it is important to recognize that from the current study no absolute specific dose recommendation can be given, considering that this was a retrospective, observational study, dosage was studied as time-averaged dose, and there may be a lost to follow-up bias. Further prospective studies are required to define optimal dosing.

In the current study, IV/SC prostanoids were discontinued for approximately one-third of the children. All were transitioned to an oral or per-inhalation treatment regimen. The number of patients discontinued from IV/SC prostanoids might seem high, which may lead to the question whether there was initial overtreatment. The patients were all initially started on IV/SC

prostanoids according to guidelines applicable at the time recommending IV/SC prostanoid initiation for patients at high risk for death or with insufficient response to nonparenteral therapy. Our results confirm that the patients in our current study cohort indeed had more advanced disease compared with the original source cohort. Furthermore, weaning from IV/SC prostanoids and transfer to oral or inhaled therapies failed for a substantial proportion of children. Based on these findings, this was not considered to qualify as initial overtreatment.

Based on time-dependent ROC analyses, criteria for durable IV/SC prostanoid discontinuation showed to identify patients for whom transition from IV/SC prostanoids to oral/inhaled therapy was safe also in the long term. These children, who were all in WHO-FC

I or II, showed excellent long-term outcome after discontinuation, in contrast to those not meeting the criteria. Even though the majority of these latter children were in WHO-FC I-II at time of discontinuation, they had poor transplant- and IV/SC prostanoid reinitiation-free survival. Therefore, transition of IV/SC prostanoid to oral/inhaled therapy should not be advocated for children not meeting the criteria, even when they are in good functional class. Although the proposed criteria have to be validated prospectively, our study highlights the important role of measuring pulmonary hemodynamics, including mPAP and PVRi, when selecting patients to be considered for IV/SC prostanoid discontinuation. In the authors' opinion, this outweighs the risks of cardiac catheterization in children in good WHO-FC (27, 28).



**Figure 3.** Transplantation-free and intravenous (IV)/subcutaneous (SC) prostanoid reinitiation-free survival from the moment of IV/SC prostanoid discontinuation of children reaching criteria for durable IV/SC prostanoid discontinuation ( $n=13$ ) and children not reaching the criteria ( $n=16$ ). One-, 3-, and 5-year survival rates after discontinuation were 100%, 100%, and 100% for the first group and 93%, 84%, and 67% for the latter group, respectively.  $P=0.027$ .

**Table 4.** Univariable Cox regression analysis for transplant-free survival in patients on continuing IV/SC prostanoids ( $n = 64$ )

	Univariable Analysis	
	Hazard Ratio (95% CI)	P Value
Age diagnosis, per year increase	1.158 (1.057–1.268)	0.002
Female sex vs. male sex	1.479 (0.627–3.488)	0.371
Hemodynamic relevant shunt-defect	0.439 (0.059–3.287)	0.423
WHO-FC III-IV vs. I-II	0.873 (0.313–2.434)	0.795
mPAP, per mm Hg increase	1.024 (1.001–1.048)	0.038
mRAP, per mm Hg increase	1.138 (1.021–1.268)	0.020
PVRI, per WU·m <sup>2</sup> increase	1.040 (1.014–1.067)	0.003
Cardiac index, per 1 L/min/m <sup>2</sup> increase	0.861 (0.662–1.121)	0.266
mPAP/mSAP, per 0.1 increase	1.156 (0.999–1.338)	0.052
Time between diagnosis and initiation of IV/SC prostanoids (month)	1.013 (0.989–1.037)	0.297
Time-averaged dose during therapy period (per 10 ng/kg/min)	0.737 (0.612–0.889)	0.001
Treatment intensity		
Dual versus monotherapy	0.292 (0.106–0.805)	0.017
Triple versus monotherapy	0.127 (0.037–0.434)	0.001

*Definition of abbreviations:* CI = confidence interval; IV = intravenous; mPAP = mean pulmonary artery pressure; mPAP/mSAP = mean pulmonary-to-systemic artery pressure ratio; mRAP = mean right atrial pressure; PVRI = pulmonary vascular resistance index; SC = subcutaneous; WHO-FC = World Health Organization functional class; WU = Wood units.

Three previous studies have reported uneventful transition from IV/SC prostanoids to oral/inhaled therapy for patients with favorable clinical status (WHO-FC I or II [9], or WHO FC I, II, or III symptoms with stable PAH [29]) and/or favorable hemodynamics (either normal or near-normal mPAP [8], or mPAP < 35 mm Hg with normal cardiac index [9]) (8, 9, 29). In these studies, however, follow-up time was short, and from these limited data, it is not possible to predict which children with PAH will benefit from a transition from IV/SC prostanoids to oral/inhaled therapy. The current study adds robust analyses based on medium- to long-term follow-up data that allowed to analyze predictors of IV/SC prostanoid discontinuation that is safe also in the long term, including relevant cut-off values for these predictors.

An important limitation of IV/SC prostanoid therapy is the occurrence of side effects, including flushes, jaw pain,

and diarrhea, but also of administration-related complications, including line infections, bacteremia, sepsis, and thrombosis (30–32). The latter can lead to systemic embolic complications in patients with right-to-left shunts owing to PAH-CHD. Also, sudden interruption of IV epoprostenol therapy may lead to potentially fatal rebound PH. For SC therapy, pain and infection of the injection site are common and may limit its use in children (23, 33). In the current study, IV/SC prostanoids had to be discontinued owing to such complications or severe side effects in 5% of the children ( $n = 5$ ). None of the children died because of administration-related complications or side effects, or accidental sudden interruption of infusion and rebound PH.

Intrinsic limitations of retrospective studies are applicable to the current study. Retrospectively determined cut-off values should be validated in prospective studies,

and robust conclusions regarding a causal relation between higher IV/SC prostanoid doses, timing of initiation, and outcome cannot be drawn. The current data were limited to the study period of 2000–2010. Follow-up data from the year 2010 onward are not available and were not included. Nevertheless, with a median follow-up duration of 4.2 years (IQR, 1.8–8.0), this study comprises some of the longest-term follow-up data in the field of pulmonary hypertension and IV/SC prostanoid therapy in children. Because the majority of patients treated with IV/SC treprostinil were also treated with epoprostenol during their follow-up time (owing to a switch from one medication to the other), data did not allow to stratify for IV/SC treprostinil versus epoprostenol treatment.

### Conclusions

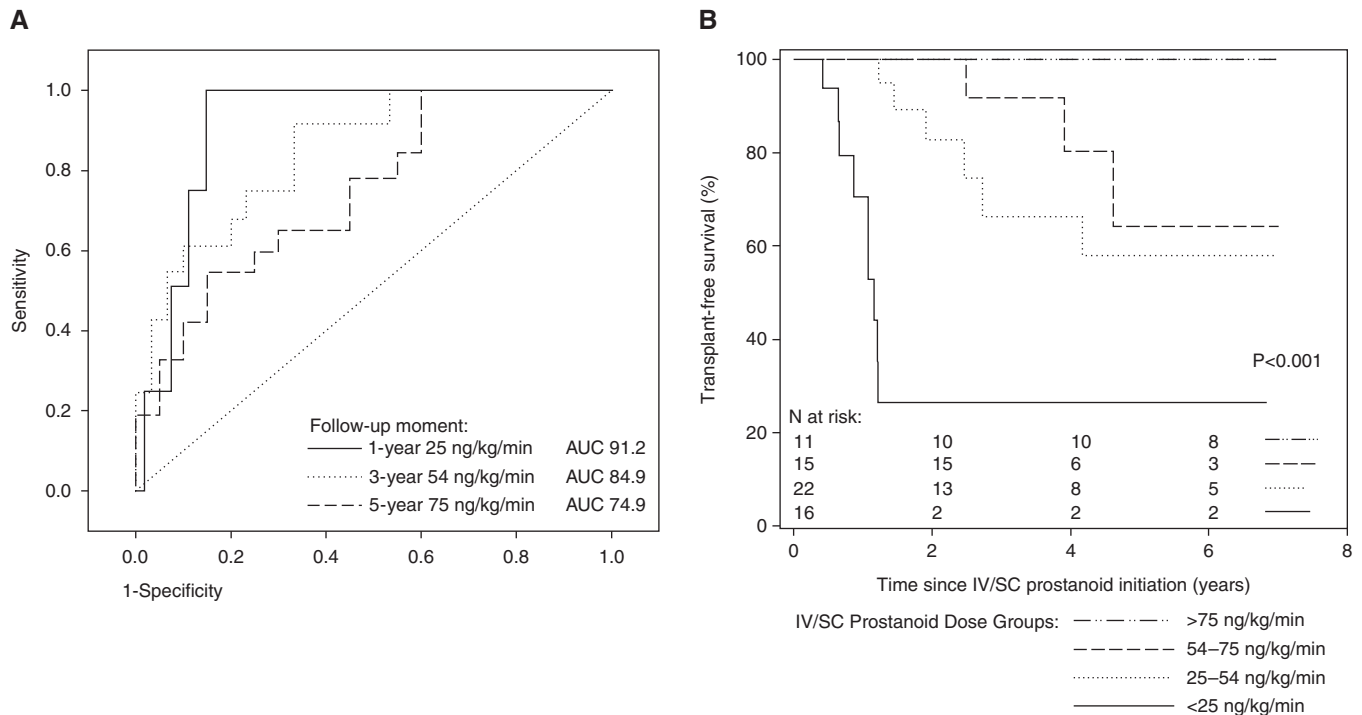
This multicenter, retrospective, observational study shows that in the

**Table 5.** Time-averaged dose cut-off values based on time-dependent ROC analysis

Follow-Up Time	Time-averaged Dose Cut Off Value*	AUC	Sensitivity	Specificity
1 Year	25 ng/kg/min	91.2	1.00	0.85
3 Years	54 ng/kg/min	84.9	0.92	0.67
5 Years	75 ng/kg/min	74.9	1.00	0.40

*Definition of abbreviations:* AUC = area under the curve; ROC = receiver operating characteristic.

\*Cut-off value selection based on the highest sum of sensitivity and specificity.



**Figure 4.** Time-dependent receiver operating characteristic (ROC) and Kaplan-Meier curve for dose. (A) Time-dependent ROC analyses for time-averaged intravenous/subcutaneous (IV/SC) prostanoid dose versus transplant-free survival at 1, 3, and 5 years of follow-up (B) Kaplan-Meier survival curve for patients grouped based on the dose cut-off values from time-dependent ROC analyses. AUC = area under the curve.

current era of PAH-targeted drugs, one-third of children with PAH were treated with IV/SC prostanoids. For these children, early initiation of IV/SC prostanoid therapy, higher doses of IV/SC prostanoids, and the combination with additional PAH-targeted therapy were all independently associated with favorable

outcome. Safe transition, also in the long term, from IV/SC prostanoid therapy to oral or inhaled therapies is possible in selected children, identified by reaching the criteria for durable IV/SC prostanoid discontinuation in addition to favorable WHO-FC while on IV/SC prostanoid therapy. ■

**Author disclosures** are available with the text of this article at [www.atsjournals.org](http://www.atsjournals.org).

**Acknowledgment:** The authors thank Theresia Vissia-Kazemier, Kathleen Miller-Reed, and Beth Coleman for their contribution to this study.

## References

- van Loon RLE, Roofthoof MTR, Hillege HL, ten Harkel ADJ, van Osch-Gevers M, Delhaas T, *et al*. Pediatric pulmonary hypertension in the Netherlands: epidemiology and characterization during the period 1991 to 2005. *Circulation* 2011;124:1755–1764.
- Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, *et al*.; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Surgery and Anesthesia; and the American Thoracic Society. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. *Circulation* 2015;132:2037–2099.
- Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, *et al*.; ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016;37:67–119.
- van Loon RLE, Roofthoof MTR, Delhaas T, van Osch-Gevers M, ten Harkel ADJ, Strengers JLM, *et al*. Outcome of pediatric patients with pulmonary arterial hypertension in the era of new medical therapies. *Am J Cardiol* 2010;106:117–124.
- Siehr SL, Ivy DD, Miller-Reed K, Ogawa M, Rosenthal DN, Feinstein JA. Children with pulmonary arterial hypertension and prostanoid therapy: long-term hemodynamics. *J Heart Lung Transplant* 2013;32:546–552.
- Barst RJ, Maislin G, Fishman AP. Vasodilator therapy for primary pulmonary hypertension in children. *Circulation* 1999;99:1197–1208.
- Lammers AE, Hislop AA, Flynn Y, Haworth SG. Epoprostenol treatment in children with severe pulmonary hypertension. *Heart* 2007;93:739–743.
- Ivy DD, Doran A, Claussen L, Bingaman D, Yetman A. Weaning and discontinuation of epoprostenol in children with idiopathic pulmonary arterial hypertension receiving concomitant bosentan. *Am J Cardiol* 2004;93:943–946.

- 9 Melnick L, Barst RJ, Rowan CA, Kerstein D, Rosenzweig EB. Effectiveness of transition from intravenous epoprostenol to oral/inhaled targeted pulmonary arterial hypertension therapy in pediatric idiopathic and familial pulmonary arterial hypertension. *Am J Cardiol* 2010;105:1485–1489.
- 10 Zijlstra WMH, Douwes JM, Rosenzweig EB, Schokker S, Krishnan U, Roofthoof MTR, *et al.* Survival differences in pediatric pulmonary arterial hypertension: clues to a better understanding of outcome and optimal treatment strategies. *J Am Coll Cardiol* 2014;63:2159–2169.
- 11 Rosenzweig EB, Abman SH, Adatia I, Beghetti M, Bonnet D, Haworth S, *et al.* Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. *Eur Respir J* 2019;53:1801916.
- 12 Montani D, Achouh L, Dorfmueller P, Le Pavec J, Sztrymf B, Tchérakian C, *et al.* Pulmonary veno-occlusive disease: clinical, functional, radiologic, and hemodynamic characteristics and outcome of 24 cases confirmed by histology. *Medicine (Baltimore)* 2008;87:220–233.
- 13 Huertas A, Girerd B, Dorfmueller P, O'Callaghan D, Humbert M, Montani D. Pulmonary veno-occlusive disease: advances in clinical management and treatments. *Expert Rev Respir Med* 2011;5:217–229, quiz 230–231.
- 14 Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, *et al.* Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013;62:D34–D41.
- 15 Gombert-Maitland M, Tapson VF, Benza RL, McLaughlin VV, Krichman A, Widlitz AC, *et al.* Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. *Am J Respir Crit Care Med* 2005;172:1586–1589.
- 16 Rubenfire M, McLaughlin VV, Allen RP, Elliott G, Park MH, Wade M, *et al.* Transition from IV epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension: a controlled trial. *Chest* 2007;132:757–763.
- 17 Ivy DD, Claussen L, Doran A. Transition of stable pediatric patients with pulmonary arterial hypertension from intravenous epoprostenol to intravenous treprostinil. *Am J Cardiol* 2007;99:696–698.
- 18 Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. *Biometrics* 2000;56:337–344.
- 19 Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001–2006. *Heart* 2009;95:312–317.
- 20 Ivy DD, Rosenzweig EB, Lemarié J-C, Brand M, Rosenberg D, Barst RJ. Long-term outcomes in children with pulmonary arterial hypertension treated with bosentan in real-world clinical settings. *Am J Cardiol* 2010;106:1332–1338.
- 21 Barst RJ, McGoan MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. *Circulation* 2012;125:113–122.
- 22 Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992;327:76–81.
- 23 Levy M, Del Cerro MJ, Nadaud S, Vadlamudi K, Colgazier E, Fineman J, *et al.* Safety, efficacy and management of subcutaneous treprostinil infusions in the treatment of severe pediatric pulmonary hypertension. *Int J Cardiol* 2018;264:153–157.
- 24 Haarman MG, Lévy M, Roofthoof MTR, Douwes JM, Vissia-Kazemier TR, Szezepanski I, *et al.* Upfront triple combination therapy in severe paediatric pulmonary arterial hypertension. *Eur Respir J* [online ahead of print] 28 Jan 2021; DOI: 10.1183/13993003.01120-2020.
- 25 Rich S, McLaughlin VV. The effects of chronic prostacyclin therapy on cardiac output and symptoms in primary pulmonary hypertension. *J Am Coll Cardiol* 1999;34:1184–1187.
- 26 Tella JB, Kulik TJ, McSweeney JE, Sleeper LA, Lu M, Mullen MP. Prostanoids in pediatric pulmonary hypertension: clinical response, time-to-effect, and dose-response. *Pulm Circ* 2020;10:2045894020944858.
- 27 Hill KD, Lim DS, Everett AD, Ivy DD, Moore JD. Assessment of pulmonary hypertension in the pediatric catheterization laboratory: current insights from the Magic registry. *Catheter Cardiovasc Interv* 2010;76:865–873.
- 28 Beghetti M, Schulze-Neick I, Berger RMF, Ivy DD, Bonnet D, Weintraub RG, *et al.*; TOPP Investigators. Haemodynamic characterisation and heart catheterisation complications in children with pulmonary hypertension: Insights from the Global TOPP Registry (tracking outcomes and practice in paediatric pulmonary hypertension). *Int J Cardiol* 2016;203:325–330.
- 29 Ivy DD, Feinstein JA, Yung D, Mullen MP, Kirkpatrick EC, Hirsch R, *et al.* Oral treprostinil in transition or as add-on therapy in pediatric pulmonary arterial hypertension. *Pulm Circ* 2019;9:2045894019856471.
- 30 Badesch DB, Tapson VF, McGoan MD, Brundage BH, Rubin LJ, Wigley FM, *et al.* Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med* 2000;132:425–434.
- 31 Dickinson MG, Schölvinc EH, Boonstra A, Vonk-Noordegraaf A, Snijder RJ, Berger RMF. Low complication rates with totally implantable access port use in epoprostenol treatment of pulmonary hypertension. *J Heart Lung Transplant* 2009;28:273–279.
- 32 Barst R. How has epoprostenol changed the outcome for patients with pulmonary arterial hypertension? *Int J Clin Pract Suppl* 2010;168:23–32.
- 33 Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, *et al.*; Treprostinil Study Group. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002;165:800–804.