CHEST

Mortality in Patients With Pulmonary Arterial Hypertension Treated With Continuous Prostanoids

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BACKGROUND: Parenteral prostanoids are considered the treatment of choice for patients with severe pulmonary arterial hypertension (PAH). Prognostic studies for patients treated in the modern era are limited.

METHODS: In this retrospective cohort study, patients initiating IV epoprostenol or IV or subcutaneous (SC) treprostinil therapy for PAH from 2007 to 2016 at UT Southwestern and The Ohio State University were included. Transplant-free survival was assessed from the time of IV/SC therapy initiation and from the time of first follow-up. The utility of traditional prognostic measures was assessed by using categories (lower, intermediate, and higher risk) recommended in the 2015 European Society of Cardiology/European Respiratory Society guidelines for functional class, 6-min walk distance, brain natriuretic peptide or N-terminal pro-brain natriuretic peptide level, and hemodynamic results.

RESULTS: Patients with group 1 PAH receiving IV epoprostenol (n = 132), IV treprostinil (n = 25), or SC treprostinil (n = 38) were included. Survival from IV/SC prostanoid initiation was 84%, 77%, and 67% at 1, 2, and 3 years. Follow-up assessment was performed after a minimum of 90 days' therapy (mean, 356 ± 247 days) in 163 patients. After treatment with an IV/SC prostanoid, better functional class, 6-min walk distance, brain natriuretic peptide/N-terminal pro-brain natriuretic peptide level, and mixed venous O_2 saturation (but not cardiac index) was associated with survival, as was the total number of lower risk and higher risk findings. Having zero lower risk findings or two or more higher risk findings was associated with particularly poor outcomes.

CONCLUSIONS: In patients with PAH receiving treatment with a parenteral prostanoid, survival was significantly associated with the number of guideline-recommended lower risk and higher risk criteria achieved at first follow-up. CHEST 2018; 154(3):532-540

KEY WORDS: biomarkers; catheterizations; pulmonary arterial hypertension

ABBREVIATIONS: 6MWD = 6-min walk distance; BNP = brain natriuretic peptide; CHD = congenital heart disease; CTD = connective tissue disease; ESC/ERS = European Society of Cardiology/European Respiratory Society; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary arterial pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SC = subcutaneous; SVI = stroke volume index; SVO_2 = mixed venous O_2 saturation; SVR = systemic vascular resistance

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Although many patients with pulmonary arterial hypertension (PAH) are now treated with oral therapies, continuous parenteral prostanoids, including epoprostenol (IV) and treprostinil (IV and subcutaneous [SC]), remain the most effective treatment for patients with advanced disease. Prognosis for these patients is guarded. Transplant consensus guidelines recommend transplant evaluation for patients initiating parenteral prostanoids and recommend transplant listing if posttreatment prognostic test results suggest an inadequate response.[1] Reassessment is generally recommended after a minimum of 3 months' therapy. However, in practicality, the definition of an "inadequate response" remains nebulous given that the data are limited regarding prognostic markers in patients undergoing advanced treatment.

Commonly used prognostic tests include functional class, 6-min walk distance (6MWD), brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) level, and invasive hemodynamic measures. This testing schedule is based on observational studies and recommendations from consensus guidelines.[2,3] Risk levels for each measure (lower, intermediate, and higher risk) have been described, and although not initially intended as a scoring system per se, an association between the total number of lower and higher risk measures and survival has been reported.[4-6] However, studies in patients initiating parenteral prostanoids are lacking.

We therefore sought to evaluate whether consensus guideline-recommended prognostic measures were associated with survival free from transplant in patients with PAH initiating parenteral prostanoids between 2007 and 2016.

Patients and Methods

This study was a retrospective trial that included patients initiating IV epoprostenol or IV or SC treprostinil therapy between 2007 and 2016 at UT Southwestern and The Ohio State University. Institutional review board approval was obtained from the UT Southwestern Medical Center Human Research Protection Program (#052015-041), including a waiver of informed consent. Patients had a confirmed group 1 PAH diagnosis with an evaluation that included echocardiogram, cardiac catheterization, pulmonary function testing, ventilation-perfusion scan, or CT angiography; diagnoses allowed included idiopathic PAH (IPAH), heritable PAH (HPAH), connective tissue disease-associated (CTD) PAH, congenital heart disease-associated (CHD) PAH, and PAH associated with HIV.

Routine PAH prognostic measures obtained for clinical purposes were recorded at two primary time points: prior to IV/SC therapy and first follow-up that included a right heart catheterization after the initiation of IV/SC therapy, performed after a minimum of 90 days of IV/SC prostanoid therapy. Other variables recorded included age, sex, PAH etiology, functional class, 6MWD, and hemodynamic variables. The hemodynamic variables reported included right atrial pressure (RAP), mean pulmonary arterial pressure (mPAP), pulmonary capillary wedge pressure, cardiac index (by thermodilution), mixed venous oxygen saturation (SVO_2), and calculated pulmonary vascular resistance (PVR). Data on heart rate, mean arterial pressure, stroke volume index (SVI), and systemic vascular resistance (SVR) were also collected, when available, but these variables were not included on all catheterization reports.

Statistical Analysis

Continuous variables were described as mean and SD or median and interquartile range. Changes between baseline and first follow-up were compared by using a paired *t* test for hemodynamic variables and the Wilcoxon signed-rank test for functional class and 6MWD. For all survival assessments, patients undergoing transplant were censored at the time of transplant.

Survival According to Risk Category

A multimodality approach to risk assessment in PAH has been recommended.[2,3,7,8] The present article used lower, intermediate, and higher risk ranges from the 2015 European Society of Cardiology and European Respiratory Society (ESC/ERS) consensus guidelines.[3] Functional class (I/II, III, and IV), 6MWD (> 440, 165-440, and < 165 m), BNP level (< 50, 50-300, and > 300 pg/mL), NT-proBNP level (< 300, 300-1400, and > 1400 pg/mL), RAP (< 8, 8-14, and > 14 mm Hg), cardiac index (≥ 2.5, 2-2.4, and < 2 L/min/m^2), and SVO_2 (> 65%, 60%-65%, and < 60%) were included.

Hazard ratios were calculated by using Cox proportional hazards methods with the lowest risk category as reference. For the individual measures, survival was assessed from IV/SC therapy initiation and from first follow-up catheterization, performed after a minimum of 90 days of IV/SC therapy. For the combined measures analysis, the association between survival from first follow-up and the total number of lower risk (zero, one, two, and three to four measures) and higher risk (zero, one, two, and three to four) measures present at this time point were assessed. Our primary hypothesis was that patients with the fewest lower risk measures and with the greatest number of higher risk measures following prostanoid treatment would have worse outcomes. For hemodynamic variables, we considered a patient with both an RAP < 8 mm Hg and a cardiac index ≥ 2.5 L/min/m^2 as meeting the lower risk criteria, whereas those with either an RAP > 14 mm Hg or cardiac index < 2 L/min/m^2 as higher risk; SVO_2 was not included in this analysis. Kaplan-Meier curves were created for survival according to etiology and survival according to number of lower and higher risk measures.

Survival: Continuous Variables Analysis

A Cox proportional hazards survival analysis was also performed assessing age, 6MWD, and hemodynamic parameters as continuous variables (RAP, mPAP, PVR, cardiac index, and SVO_2) along with functional class, sex, and PAH etiology (CTD vs not). Due to a higher rate of missing data, NT-proBNP was excluded from the primary multivariate analysis but was included in an exploratory model. An additional exploratory analysis evaluating cardiac index, SVI, and hemoglobin was also completed, based on the lack of an association between cardiac index and outcome in the initial analyses. Variables were entered in a stepwise forward manner and were retained in the model if there was a significant difference ($P < .05$) in the log likelihood between the models at each step using the likelihood ratio test. Variables with a P value > .05 were removed from the multivariable model. NCSS 11 Statistical Software (NCSS, LLC) was used for the analyses.

Results

The study population included 195 patients with group 1 PAH that was idiopathic, heritable, or associated with CTD, CHD, or HIV (Fig 1, Table 1). Patients received IV epoprostenol (n = 132), IV treprostinil (n = 25), or SC treprostinil (n = 38), initiated a median of 454 days from diagnosis. Forty-two patients (22%) were treatment naive at the time of IV/SC therapy initiation; the remainder were undergoing treatment with one, two, or three PAH therapies at initiation. Survival from the time of IV/SC prostanoid initiation was 84%, 77%, and 67% at 1, 2, and 3 years, respectively; survival according to PAH subgroup is shown in Figure 2.

Among patients with paired results for pre- and post-IV/SC therapy, there was significant improvement in all major prognostic measures, including hemodynamic variables, 6MWD, and functional class (Table 2). The mean improvement in PVR was 39 ± 34% ($P < .001$). Mean arterial pressure and SVR decreased as well; posttreatment SVR was not associated with prostanoid type or dose but was lower in those receiving triple combination therapy (e-Fig 1). Epoprostenol dose at the time of first follow-up right heart catheterization was 33 ± 12 ng/kg/min, and the treprostinil dose was 45 ± 17 ng/kg/min. Most patients were also receiving one (35%) or two (61%) oral medications at this time point.

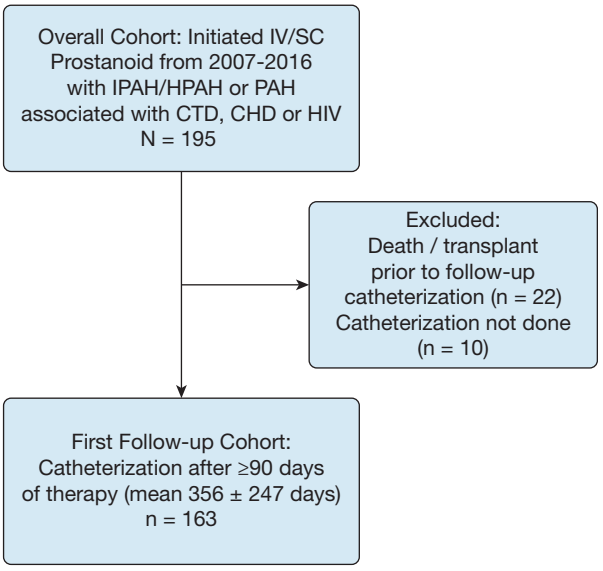

Figure 1 – *Patients with PAH. CTD = connective tissue disease; CHD = congenital heart disease; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension.*

TABLE 1] Patient Demographic Characteristics and Hemodynamic Variables at Diagnosis

	Combined Group (N = 195)
Age at diagnosis, y	45 ± 14 (range, 9-76)
Female sex	84%
Etiology[a]	
Idiopathic PAH	111
Heritable PAH	9
Connective tissue disease	61
Congenital heart disease	12
HIV	2
Hemodynamic variables at diagnosis	
Right atrial pressure, mm Hg	13 ± 7
Mean pulmonary arterial pressure, mm Hg	55 ± 11
Wedge, mm Hg	11 ± 8
Cardiac output, L/min	4.0 ± 1.4
Cardiac index, L/min/m^2	2.1 ± 0.7
Stroke volume index, mL/m^2	31 ± 11
SVO_2, %	57 ± 11
Pulmonary vascular resistance, Wood units	12.0 ± 5.5
Mean arterial pressure[b]	91 ± 13
Systemic vascular resistance[b]	1,510 ± 640
PAH medications prior to IV/SC therapy initiation	
0	42 (22%)
1	53 (27%)
2	56 (29%)
3	44 (23%)
Time from diagnosis to IV treatment start (median, 454 d)	
< 3 mo	56 (29%)
3 mo-2 y	63 (32%)
2-4 y	42 (22%)
> 4 y (maximum, 13 y)	34 (17%)
IV/SC therapy	
IV epoprostenol	132 (68%)
IV treprostinil	25 (13%)
SC treprostinil	38 (19%)

PAH = pulmonary arterial hypertension; SC = subcutaneous; SVO_2 = mixed venous O_2 saturation.

[a]Drug/toxin-induced pulmonary hypertension is not included as a separate category; prior amphetamine, methamphetamine, or cocaine use was reported in 26 patients (idiopathic PAH: n = 19: heritable PAH: n = 3; connective tissue disease-associated: n = 3; HIV-associated PAH: n = 1).

[b]n = 96.

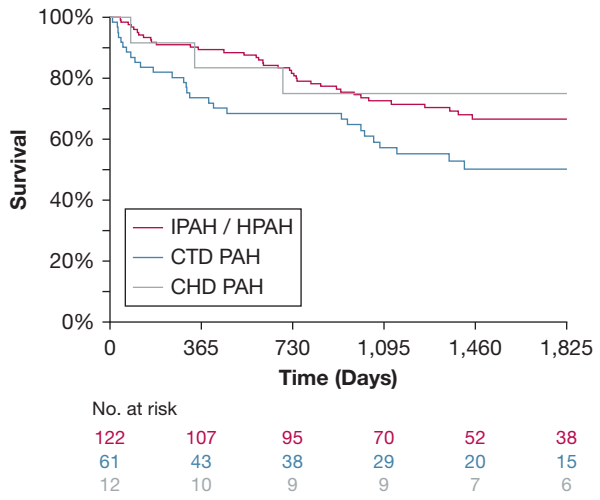

Figure 2 – *Survival from time of initiation of IV/subcutaneous therapy. Overall survival at 1, 2, and 3 years was 84%, 77%, and 67%, respectively. Patients with CTD-associated PAH had lower survival rates compared with the IPAH/HPAH group, and this finding approached statistical significance (hazard ratio, 1.56; P = .058). See Figure 1 legend for expansion of abbreviations.*

Prognosis: ESC/ERS Guideline Measures

Hazard ratios for mortality from the time of first follow-up catheterization for patients classified as lower, intermediate, and higher risk for each individual measure are shown in Tables 3 and 4. Higher risk functional class, 6MWD, and BNP/NT-proBNP category were associated with mortality from the time of IV/SC therapy initiation and from first follow-up assessment. In contrast, hemodynamic variables were associated with outcome only from first-follow-up, with posttreatment SVO_2 ($P = .02$) and RAP ($P = .06$) but not cardiac index reaching or approaching statistical significance.

We next evaluated transplant-free survival from first follow-up according to the following: (1) total number of lower risk criteria; and (2) total number of higher risk criteria (ESC/ERS guidelines). Both models were associated with outcomes (Figs 3A and 3B), and survival rates were ≤ 50% at 2 years for patients with zero lower risk measures at first follow-up (n = 39) and for those with two or more higher risk measures at follow-up (n = 25).

Univariate and Multivariate Analyses

Univariate and multivariate analyses were completed to further investigate the association between first follow-up prognostic measures and mortality. Measures included are shown in Table 5. In the univariate analysis,

TABLE 2] Hemodynamic Variables, Walk Data, and Functional Class Before and After IV/SC Therapy

Variable	Pre-IV/SC Therapy	First Follow-Up	*P* Value
Catheterization (n = 160)			
Days[a]		356 ± 247	
RAP, mm Hg	13 ± 7	8 ± 6	< .001
mPAP, mm Hg	56 ± 12	46 ± 12	< .001
Wedge, mm Hg	10 ± 5	10 ± 5	.37
PVR, Wood units	12 ± 5	7 ± 3	< .001
Cardiac index, L/min/m^2	2.2 ± 0.7	3.2 ± 0.9	< .001
SVI, mL/m^2	31 ± 11	36 ± 11	< .001
SVO_2, %	57 ± 10	66 ± 8	< .001
MAP, mm Hg[b]	92 ± 13	84 ± 12	< .001
SVR, dynes/s/cm^5[b]	1,500 ± 650	1,070 ± 380	< .001
Walk (n = 124)			
Mean, m	267 ± 135	337 ± 121	< .001
Median, m	290	345	
WHO functional class (n = 161)			
I/II	9	61	< .001
III	71	72	
IV	81	28	

MAP = mean arterial pressure; mPAP = mean pulmonary arterial pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SVI = stroke volume index; SVR = systemic vascular resistance; WHO = World Health Organization. See Table 1 legend for expansion of other abbreviations.
[a]Days from IV/SC therapy initiation to follow-up assessment.
[b]n = 95. Patients without results at both time points were excluded.

TABLE 3] Pre-Prostanoid Therapy: Prognosis According to ESC/ERS Lower, Intermediate, and Higher Risk Categories

Variable	No.	Hazard Ratio for Mortality	*P* Value	χ^2 Model
Functional class	(179)			
II	9	1	< .05	8.1
III	81	1.2 (0.3-5.1)		
IV	89	2.4 (0.6-10.0)		
6MWD, m	(156)			
> 440	11	1	< .05	9.2
165-440	102	1.1 (0.3-3.5)		
< 165	43	2.4 (0.7-7.8)		
BNP/NT-proBNP, ng/L[a]	(158)			
< 50/< 300	18	1	< .05	6.9
50-300/300-1,400	39	1.2 (0.4-3.8)		
> 300/> 1,400	101	2.4 (0.8-6.6)		
RAP, mm Hg	(185)			
< 8	45	1	.57	1.2
8-14	75	1 (0.6-1.9)		
> 14	65	1.3 (0.7-2.4)		
Cardiac index, L/min/m^2	(181)			
≥ 2.5	59	1	.32	2.3
2-2.4	47	1.5 (0.8-2.8)		
< 2	75	1.4 (0.8-2.4)		
SVO_2, %	(168)			
> 65	41	1	.51	1.4
60-65	28	1.2 (0.5-2.8)		
< 60	99	1.4 (0.8-2.6)		

6MWD = 6-min walk distance; BNP = brain natriuretic peptide; ESC/ERS = European Society of Cardiology/European Respiratory Society; NT-proBNP = N-terminal pro-brain natriuretic peptide. See Table 1 and 2 legends for expansion of other abbreviations.
[a]If both were available, NT-proBNP was used. Hazard ratios for risk of mortality are shown for each measure, using the lowest risk category as the reference.

age, RAP, mPAP, SVO_2, 6MWD, functional class, and log NT-proBNP, but not cardiac index, were associated with mortality. In the primary multivariate analysis, male sex, SVO_2, 6MWD, and functional class IV were associated with outcome; in the exploratory model (NT-proBNP added), male sex, RAP, functional class IV, and log NT-proBNP were associated.

Finally, the relationship between cardiac index, SVI, and mortality was explored. There was no association between mortality and cardiac index stratified according to quartile (e-Fig 2) or mortality and cardiac index or SVI as continuous variables. However, the associations with cardiac index and SVI approached statistical significance after adjustment for hemoglobin levels (cardiac index HR, 0.73 [95% CI, 0.5-1.06], $P = .1$; SVI HR, 0.97 [95% CI, 0.94-1.001], $P = .051$), respectively) (e-Table 1).

Discussion

In this study that included patients with group 1 PAH initiating treatment with a continuous IV or SC prostanoid, the total number of posttreatment lower risk and higher risk prognostic variables was significantly associated with outcome using four routine assessments: functional class, 6MWD, BNP or NT-proBNP level, and hemodynamic variables (mRAP and cardiac index, specifically). We found a particularly high mortality risk for patients without any lower risk criteria (n = 39) and for those with two or more higher risk criteria at first follow-up (n = 25). Similar strategies have recently been shown to be useful in assessing prognosis in PAH in general, including IPAH/HPAH in a French registry cohort[5] and group 1 PAH in the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) and a Swedish

TABLE 4] First Follow-Up Assessment: Prognosis According to ESC/ERS Lower, Intermediate, and Higher Risk Categories

Variable	No.	Hazard Ratio for Mortality	*P* Value	χ^2 Model
Functional class	(n = 152)			
I or II	61	1	< .001	24.1
III	74	2.1 (1.04-4.1)		
IV	28	6.6 (3.1-14.1)		
6MWD, m	(n = 144)			
> 440	28	1	< .01	14.0
165-440	103	3.1 (1.1-8.7)		
< 165	13	9.3 (2.7-31.8)		
BNP/NT-proBNP, ng/L[a]	(n = 149)			
< 50/< 300	42	1	< .001	27.9
50-300/300-1,400	59	2.4 (0.9-6.0)		
> 300/> 1,400	45	6.9 (2.9-16.7)		
RAP, mm Hg	(n = 163)			
< 8	84	1	.06	5.7
8-14	56	1.5 (0.8-2.6)		
> 14	23	2.3 (1.2-4.6)		
Cardiac index, L/min/m^2	(n = 163)			
≥ 2.5	129	1	.73	0.6
2-2.4	27	0.8 (0.4-1.7)		
< 2	7	1.3 (0.5-3.6)		
SVO_2, %	(n = 163)			
> 65	91	1	.02	7.6
60-65	35	1.8 (0.9-3.3)		
< 60	37	2.2 (1.2-4.0)		

See Table 1, 2, and 3 legends for expansion of abbreviations.
[a]If both tests were done, NT-proBNP was used. Hazard ratios for risk of mortality are shown for each measure, using the lowest risk category as the reference.

registry.[4,6] However, only a small number of patients receiving prostanoids (parenteral or otherwise) were included in these studies, and outcomes according to ESC/ERS risk criteria for this patient population have not been reported.

Although replication in additional cohorts is needed, strengths of the present study are the inclusion of all patients newly started on parenteral prostanoids (including multiple PAH subtypes), both parenteral prostanoids currently available in the United States, and both treatment naive as well as patients transitioning to parenteral therapy. This approach suggests that these findings are likely broadly applicable to patients with PAH being treated with parenteral prostanoids. In addition, 97% of patients were receiving combination therapy at first follow-up, reflecting the more frequent use of combinations of medications in the modern era.

Current lung transplantation guidelines recommend parenteral prostanoids prior to active listing for lung transplantation, with a goal of delaying or avoiding transplant in some patients. Early long-term observational studies of IV epoprostenol supported this recommendation, with survival rates of approximately 50% at 5 years for treatment naive patients with IPAH/HPAH who were starting therapy.[9,10] However, later studies that included patients failing nonparenteral therapies found shorter survival times.[11,12] In the present study in which 78% of patients received other PAH therapies prior to initiating a systemic prostanoid, the 5-year survival from the time of IV therapy was 68% in IPAH/HPAH and 59% in CTD-PAH, suggesting that a trial of IV/SC therapy is still appropriate in most patients being considered for transplant referral, as long as close monitoring is practiced.

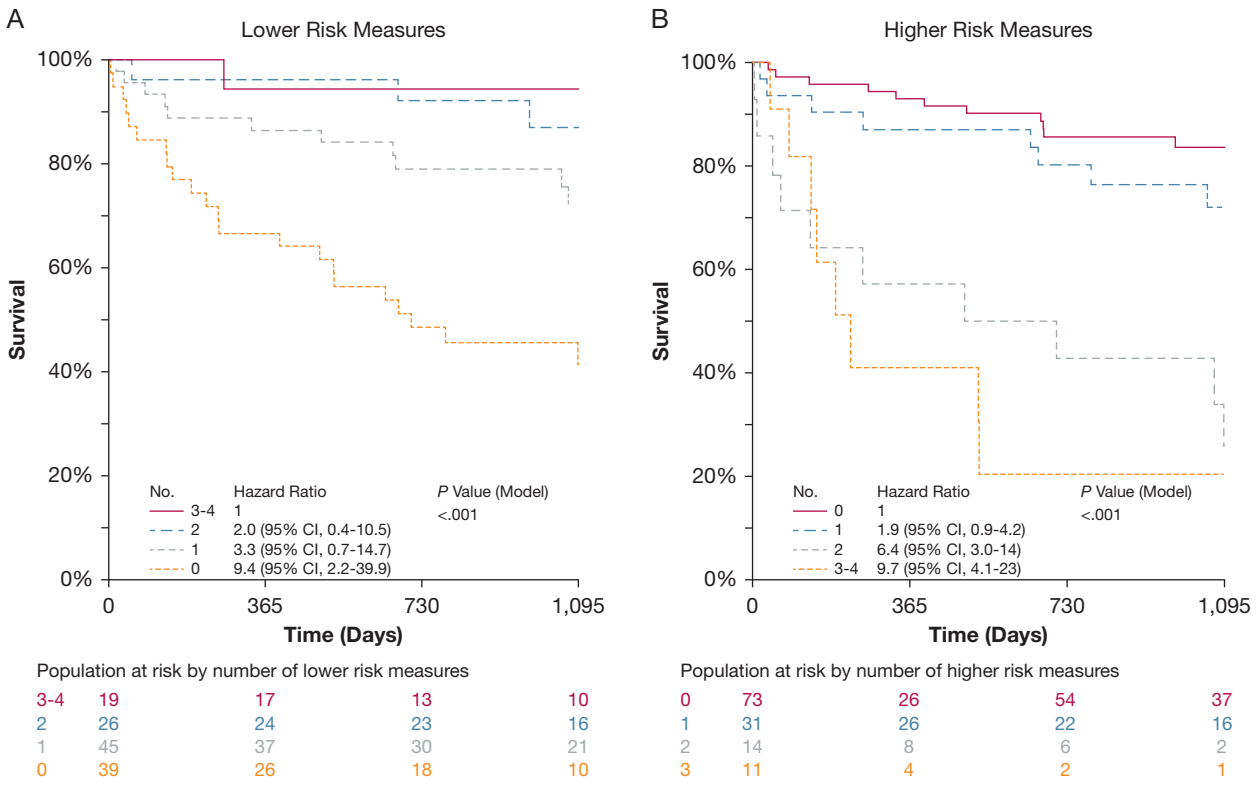

Figure 3 – *Survival according to number of (A) lower and (B) higher risk prognostic measures per European Society of Cardiology/European Respiratory Society guidelines.*

Significant improvement was seen between baseline and first follow-up in functional class, 6MWD, NT-proBNP level, and hemodynamic measures (including RAP, mPAP, PVR, cardiac index, SVI, and SVO_2). Most of these measures were also associated with outcome at first-follow-up in the univariate analyses, including three hemodynamic variables: RAP, mPAP, and SVO_2. Notably, first follow-up cardiac index was not associated with survival, despite its status as a traditionally strongly associated prognostic measure, and the association with

TABLE 5] Univariate and Stepwise Multivariate Survival Models From Time of First Follow-Up

Variable	Univariate HR (95% CI)	*P* Value	Model No. 1 (All Variables Except log NT-BNP), n = 137	*P* Value	Model No. 2 (Add log NT-BNP), n = 115	*P* Value
Age	1.03 (1.01-1.05)	< .01				
Male sex	1.47 (0.72-3.03)	.29	2.69 (1.23-5.84)	< .01	2.95 (1.29-6.76)	< .05
CTD-PAH (vs not)	1.27 (0.74-2.18)	.38				
RAP	1.06 (1.02-1.11)	< .01			1.06 (1.01-1.12)	< .05
mPAP	1.02 (1.00-1.05)	< .05				
PVR	1.06 (0.98-1.14)	.18				
Cardiac index	0.95 (0.73-1.25)	.72				
SVO_2	0.96 (0.93-0.98)	< .01	0.96 (0.93-0.99)	< .01		
6MWD	0.99 (0.992-0.997)	< .001	0.99 (0.992-0.998)	< .001		
FC III (vs II)	2.14 (1.07-4.25)	< .05				
FC IV (vs II)	6.66 (3.14-14.15)	< .001	2.81 (1.14-6.94)	< .05	2.57 (1.10-6.01)	< .05
Log NT-proBNP	2.52 (1.79-3.54)	< .001			2.31 (1.58-3.38)	< .001

Test completion rates: catheterization, n = 163; functional class, n = 153; walk, n = 141; and NT-proBNP, n = 117. CTD = connective tissue disease; FC = functional class. See Table 1, 2, and 3 legends for expansion of other abbreviations.

SVI only approached statistical significance. This outcome contrasts with the recent study by Weatherald et al,[13] which found that posttreatment RAP and SVI were the most important hemodynamic predictors of outcome in idiopathic PAH. Potential differences in the present study include the patient population (group 1 PAH vs idiopathic), the longer disease duration, and, particularly, the type of PAH therapy (with the present study including only patients undergoing IV/SC treatment). These findings suggest that additional prognostic studies focused on the IV/SC therapy population are needed. Notably, an analysis of outcomes for patients with IPAH on the lung transplant wait-list found that most current lung allocation score equation prognostic measures including both RAP and mPAP fail to predict outcomes in the pretransplant patient population, further highlighting the need for additional study of patients with PAH with advanced disease.[14]

Cardiac Index and Survival

Although the cause for the lack of a significant association between cardiac index and survival in the present study is unclear, there are several potential contributors. First, the mean posttreatment cardiac index in this study was 3.2 $\pm$ 0.9, higher than the values reported in previous monotherapy studies of epoprostenol and treprostinil (cardiac index: 2.2-2.85 L/min/m^2).[9,10,15] With most patients (79%) having a normal or near-normal cardiac index at first follow-up catheterization (cardiac index $>$ 2.5 L/min/m^2), it may be more difficult to detect an association. Second, anemia has been associated with both PAH medications and PAH severity, and could contribute to a higher cardiac index, even in the setting of significant right ventricular dysfunction.[16,17] The finding that the associations between cardiac index and SVI and survival approached statistical significance after adjusting for hemoglobin level supports this factor as a contributor. Finally, prostanoid-mediated systemic vasodilation could also potentially contribute to higher cardiac index results. This idea is supported by the lower SVR values recorded at first follow-up, where the mean SVR was only 1,070 dynes/s/cm^5, and $>$ 20% had an SVR $<$ 800 dynes/s/cm^5.

Increases in cardiac index to the point of causing high output heart failure have been reported in patients receiving IV epoprostenol at higher doses (mean, 98 $\pm$ 61 ng/kg/min).[18] Although the mean prostanoid doses used in this study (33 $\pm$ 12 ng/kg/min for epoprostenol and 45 $\pm$ 17 ng/kg/min for treprostinil) are within commonly prescribed dosing ranges,[19] it is possible that prostanoid-associated increases in cardiac index may still occur in some patients, particularly when used in combination with one or more additional PAH therapies. Randomized studies evaluating prostanoid dosing strategies are lacking, but in an observational study of epoprostenol monotherapy, there was no difference in outcomes according to era for patients treated with higher doses (1991-1997: average dose, 43 $\pm$ 35 ng/kg/min) compared with lower doses (1998-2001: average dose, 22 $\pm$ 11 ng/kg/min) (both doses are at first follow-up).[9]

Overall, our findings suggest that the strength and usefulness of some individual prognostic measures may differ for prostanoid-treated patients with PAH, particularly with combination PAH therapy. In particular, our results suggest that use of RAP and the cardiac index as the major criteria considered in lung allocation score appeals (appeals to achieve higher wait list priority) may need to be reevaluated or at least combined with other measures.[1] An updated lung allocation score equation was introduced in the United States in February 2015, but data on its performance are not yet available.[14]

Study Limitations

As a retrospective study with non-protocolized follow-up, data were missing for some variables. Patients lacking complete data were included in individual analyses to minimize potential bias but were excluded from the combined analyses. Although no significant differences at baseline were seen in these patients (demographic characteristics and prognostic measures), some differences in measures not assessed may still have been present. We were also limited in our ability to assess outcomes according to number of PAH therapies and by prostanoid dosing, as we typically added therapy and/or increased prostanoid doses in response to inadequate early responses. Finally, although we included patients with IPAH, CTD, CHD, and HIV-associated PAH, the sample size for individual subgroups was small.

Conclusions

In patients with PAH receiving a parenteral prostanoid undergoing posttreatment assessment, the best survival times were seen in patients with multiple lower risk ESC/ERS guideline criteria at follow-up. Patients with no lower risk criteria and patients meeting two or more higher risk criteria at follow-up had poor long-term outcomes, with 2-year survival rates $<$ 50%.

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Additional information: The e-Figures and e-Table can be found in the Supplemental Materials section of the online article.

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