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Prognostic factors associated with increased survival in patients with pulmonary arterial hypertension treated with subcutaneous treprostinil in randomized, placebo-controlled trials

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BACKGROUND: Because of the challenges associated with conducting large survival studies of patients with pulmonary arterial hypertension (PAH), we analyzed the surrogate markers predictive of long-term survival in a large cohort of patients treated with subcutaneous treprostinil.

METHODS: A retrospective review was conducted using data from a total of 811 patients with New York Heart Association Functional Class (NYHA FC) II to IV PAH, who were treated with subcutaneous treprostinil. Patient baseline disease and on-treatment parameters were analyzed by uni- and multivariate analyses for predictive value of 3-year survival with PAH.

RESULTS: Among the baseline disease-related factors analyzed, there was a significantly higher risk of death ($p < 0.001$) associated with connective tissue disease–associated PAH relative to idiopathic PAH (hazard ratio for death [HR] 1.93), NYHA FC IV vs III (HR 2.31), pulmonary vascular resistance index (PVRI) >30 vs ≤16 mm Hg/liter/min/m^2 (HR 2.44) and mixed venous oxygen saturation (SVO_2) ≤55% vs >55%. The 6-minute walk distance (6MWD) of ≤295 m after 12 weeks of treprostinil treatment was associated with reduced survival at 3 years (58%). A ≥20-m increase from baseline in 6MWD was associated with greater survival (80%) vs smaller walk increments (69%; $p = 0.039$). Treprostinil dose of ≥40 ng/kg/min ($p < 0.001$) and every 10-ng/kg/min dose increase ($p = 0.009$) resulted in improved long-term survival. In a multivariate analysis, only SVO_2, 6MWD and treprostinil dose were significant on-treatment predictors ($p < 0.02$) of survival.

CONCLUSIONS: Disease etiology, baseline factors (NYHA FC, PVRI and SVO_2) and on-treatment factors (6MWD, SVO_2 and treprostinil dose) were predictors of survival in this study and may be used to aid in treatment optimization.

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Pulmonary arterial hypertension (PAH) is a rare but debilitating disease characterized by a progressive increase in pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), ultimately leading to right ventricular failure and death.[1] To further characterize the prognosis of patients diagnosed with this disease, the National Institutes of Health (NIH) established a registry to follow 194 patients with idiopathic pulmonary arterial hypertension (IPAH) over a 5-year period.[2] They found that median survival for patients not receiving therapy was 2.8 years, with survival rates of 68%, 48% and 34% at 1, 3 and 5 years, respectively. Since the publication of these findings, 8 new targeted therapies for PAH have been introduced and

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shown to improve exercise capacity and hemodynamics and to delay time to disease progression.[3–11] In addition, although the aforementioned trials were not comparative by design, many of these agents have been associated with improved survival relative to the NIH registry.[12]

Although the prognosis of patients with PAH appears to have improved since the introduction of targeted therapy, ethical constraints (e.g., lack of placebo arm) have limited the ability to conduct large, prospective survival trials.[13] As a result, specific patient-related characteristics and disease factors have been used to formulate a prognosis and treat PAH despite, in many cases, their lack of clinical validity or accuracy as prognostic factors.[14] Indeed, based on an equation developed by the NIH, mean PAP (mPAP), mean right atrial pressure (mRAP) and cardiac index (CI) have been defined as significant predictors of treatment-free survival.[2] In fact, a contemporary equation that may replace the NIH registry formula found these same variables as being most predictive.[15] In addition, hemodynamic data continue to be widely used to predict survival. Several studies have since identified specific baseline and on-treatment variables associated with survival in PAH,[8,16–20] most of which are associated (in some degree) with right ventricular function. The most commonly reported predictors of survival are 6-minute walk distance (6MWD), functional class (FC), mRAP, mPAP, PVR and CI; however, the prognostic value of mPAP, PVR and CI has varied by study.[8,16,17,19]

Because of ethical concerns and added challenges (e.g., sample size) of conducting well-controlled survival trials in PAH, identification and analysis of surrogate markers to predict survival is paramount. Assessing treatment outcomes across different markers of disease severity can guide optimal use of therapies, underscoring the importance of specific threshold values. The purpose of this study was to identify baseline and on-treatment prognostic factors associated with increased long-term survival using a large database of 811 patients with PAH receiving subcutaneous (SC) treprostinil in randomized, placebo-controlled trials.

Methods

Population description

This was a retrospective analysis of patients who were enrolled in 3 trials (P01: 04, 05, 06) of SC treprostinil treatment for PAH between June 25, 1998 and December 1, 2003.[7,21,22] All non-chronic thromboembolic pulmonary hypertension (non-CTEPH) subjects enrolled in the open-label trial of SC treprostinil were included in the analysis, and all patients were on treprostinil therapy. Patients were followed for as long as they received treprostinil and were censored at the time of discontinuation. Likewise, those patients who received other prostanoid therapies were discontinued from treprostinil on or near the date of initiation.

Patient eligibility criteria included: (1) age ≥8 years; (2) New York Heart Association (NYHA) FC II, III or IV; (3) IPAH (including heritable PAH and PAH associated with anorexigen use) or PAH associated with connective tissue disease (CTD), congenital heart disease (CHD) defined as repaired congenital systemic to pulmonary shunts or portal hypertension; (4) mPAP ≥25 mm Hg; (5) mean pulmonary capillary wedge pressure ≤15 mm Hg; (6) PVR >3 Wood units; and (7) 6MWD of 50 to 450 m. Patients who were on placebo for 12 weeks in the blinded trial of SC treprostinil were given the opportunity to receive treprostinil (open-label) during the long-term study period.

Study design

This retrospective review of the SC treprostinil database evaluated the association of prospective variables with long-term survival (3 years) in PAH. Baseline factors analyzed included: patient age; body mass index (BMI); disease etiology; NYHA FC; hemodynamics; and albumin, sodium, bilirubin and creatinine levels. At 12 weeks of SC treprostinil treatment, the treprostinil dose was analyzed for a correlation with 3-year survival. Additional efficacy data, including 6MWD and hemodynamics, were available at 12 weeks for 399 patients (49%), as specified by study protocols from the previously mentioned randomized, controlled trials of SC treprostinil (12-week NYHA FC data were not available).

Statistical analysis

Data from all treprostinil-treated patients were included in the analyses. Baseline was defined as the time at which the patient received his or her first dose of treprostinil (during the blinded study for the treprostinil group and during the open-label study for the placebo group and de novo patients). To establish a true pre-treprostinil baseline, all reported baseline values for each variable are the last observed value prior to treatment with treprostinil. Demographic variables are reported as the mean ± standard deviation. Individual Cox proportional hazard models were fit to survival time from initiation of treprostinil as a function of each potential predictor variable. Patients were not censored after lung transplantation. The individual predictive power of each variable was assessed using the resulting nominal p-values by Wald's test. Results are further expressed as hazard ratios with 95% confidence intervals from these models. For continuous variables, the hazard ratios (HRs) express the relative hazard for the specified incremental increase in the value of the variable. For categorical variables, the HRs express the relative hazard between each given category and the specified reference category. Based on the results of these analyses, further Cox proportional hazard models were fit to survival time as a function of various groupings of important predictor variables to assess their simultaneous predictive power for survival.

Results

Baseline characteristics

Of the 811 patients in this analysis, 628 (77%) were female, and the mean age was 45 (range 5 to 83) years. The most common diagnosis was IPAH (52%, $n = 425$). Patients in the database were NYHA FC II (16%, $n = 126$), NYHA FC III (76%, $n = 614$) and NYHA FC IV (9%, $n = 71$) at baseline. Twenty-three percent (186 of 811) of the patients were on concomitant PAH medications, including another prostanoid (8%, which includes patients transitioning to intravenous epoprostenol and patients on concomitant in-

haled iloprost or oral beraprost), bosentan (12%) and sildenafil (3%). Hemodynamics and 6MWD were characterized at baseline for 399 patients. Mean baseline values were obtained for the following hemodynamic parameters: mRAP (9.6 mm Hg); PVR (14.7 mm Hg/liter/min); PVRI (25.3 mm Hg/liter/min/m^2); CI (2.4 liters/min/m^2); and mixed venous oxygen saturation (SVO_2; 61.7%). The mean 6MWD (standard deviation) at baseline was 333 (83) m. All 11 patients who received transplantation were discontinued from treprostinil on the day of transplant. Baseline characteristics are summarized in Table 1.

Week 12 on-treatment results

After 12 weeks of treprostinil treatment, changes in hemodynamic parameters and 6MWD were determined (Table 2). Mean values for hemodynamic parameters at Week 12 were as follows: mRAP 9.9 mm Hg; PVR 14.2 mm Hg/liter/min; CI 2.4 liters/min/m^2; and SVO_2 62.5%. The mean (standard deviation) 6MWD increased by 10 (63) m at Week 12. Patients received a mean (SD) treprostinil dose of 8.3 (5.9) ng/kg/min at 12 weeks.

Table 1 Patient Demographics and Baseline Characteristics

Parameter	Patients (N = 811)
Patients enrolled from blinded study, *n* (%)	399 (49)
Placebo	209
SC treprostinil	190
Mean age (range), years	45 (5–83)
Female, *n* (%)	628 (77)
PAH etiology, *n* (%)	
IPAH	425 (52)
APAH	386 (48)
CTD	166 (20)
CHD	177 (22)
PoPH	43 (5)
NYHA FC, *n* (%)	
II	126 (16)
III	614 (76)
IV	71 (9)
Concomitant PAH medication, *n* (%)	186 (23)
Alternative prostanoid[a]	67 (8)
Bosentan	99 (12)
Sildenafil	24 (3)
Time (mean ± SD) since diagnosis of PAH, years	3.5 ± 6.3
Hemodynamics (mean ± SD)	
mRAP, mm Hg	9.6 ± 5.5[b]
PVR, mm Hg/liter/min	14.7 ± 8.3[c]
PVRI, mm Hg/liter/min/m^2	25.3 ± 13.3[c]
CI, liters/min/m^2	2.4 ± 0.9[d]
SVO_2, %	61.7 ± 10.5[e]
6MWD (mean ± SD), m	333 ± 83

APAH, associated PAH; CHD, congenital heart disease; CI, cardiac index; CTD, connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension; mRAP, mean right atrial pressure; NYHA FC, New York Heart Association functional class; PAH, pulmonary arterial hypertension; PoPH, portopulmonary hypertension; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; SC, subcutaneous; SD, standard deviation; 6MWD, 6-minute walk distance; SVO_2, mixed venous oxygen saturation.

[a]Patients received concomitant inhaled iloprost (10%) or oral beraprost (6%) or were transitioned to intravenous epoprostenol (84%).

[b]n = 384; [c]n = 335; [d]n = 371; [e]n = 346.

Table 2 On-treatment Results at Week 12

Parameter	*n*	Value (mean ± SD)
Treprostinil dose, ng/kg/min	811	8.3 ± 5.9
6MWD, m	391	354 ± 89
Hemodynamics		
mRAP, mm Hg	390	9.9 ± 6.1
PVR, mm Hg/liter/min	354	14.2 ± 8.3
PVRI, mm Hg/liter/min/m^2	354	24.2 ± 12.8
CI, liters/min/m^2	379	2.4 ± 0.9
SVO_2, %	365	62.5 ± 10.2

CI, cardiac index; mRAP, mean right atrial pressure; 6MWD, 6-minute walk distance; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; SD, standard deviation; SVO_2, mixed venous oxygen saturation.

Predictors of survival

Baseline patient-related predictors

In this analysis, specific patient-related factors were calculated as baseline predictors of disease-related death and are summarized in Table 3. Among the 811 patients, there was a significant decrease in long-term survival ($p < 0.001$) for every 10-year increase in age and for a 10-kg/m^2 decrease in BMI ($p = 0.005$). Likewise, patients with lower serum albumin (by 0.5 g/dl, $p < 0.001$) and lower sodium levels (by 5 mmol/liter, $p = 0.001$) were also found to be at greater

Table 3 Univariate Patient-related Predictors of Survival Measured at Baseline

Prognostic factor	*n*	Hazard ratio for death (95% CI)	*p*-value
Age, ↑ 10 y	811	1.20 (1.08–1.33)	<0.001
BMI, ↑ 10 kg/m^2	801	0.68 (0.52–0.89)	0.005
Disease etiology (vs IPAH)	811		<0.001[a]
CTD		1.93 (1.36–2.75)	<0.001
CHD		0.55 (0.34–0.91)	0.020
PoPH		1.36 (0.63–2.96)	0.431
Albumin, ↑ 0.5 g/dl	757	0.63 (0.53–0.74)	<0.001
Sodium, ↑ 5 mmol/liter	787	0.68 (0.55–0.86)	0.001
Total bilirubin, ↑ 0.1 mg/dl	773	1.03 (1.01–1.04)	<0.001
Creatinine, ↑ 0.5 mg/dl	785	1.96 (1.54–2.48)	<0.001
6MWD, ↑ 20 m	399	0.93 (0.89–0.98)	0.002

BMI, body mass index; CHD, congenital heart disease; CI, confidence interval; CTD, connective tissue disease; 6MWD, 6-minute walk distance; IPAH, idiopathic pulmonary arterial hypertension; PoPH, portopulmonary hypertension.

[a]Any etiology (i.e., CTD, CHD and PoPH vs IPAH).

risk of death. Increases in total bilirubin (by 0.1 mg/dl, $p < 0.001$) and creatinine (by 0.5 mg/dl, $p < 0.001$) levels also correlated with a greater risk of death. Importantly, certain disease etiologies were associated with a reduced survival rate. The 3-year survival rates among patients with CTD (50%) and IPAH (73%) were lower than for patients with CHD (87%).

Baseline disease-related predictors

Symptom severity, as assessed by functional classification, is often associated with an increased risk of disease-related death. As expected, patients in NYHA FC IV were at higher risk of death, with a 3-year survival rate of 53%, compared with patients in FC III and FC II, who had survival rates of 72% and 80%, respectively (Figure 1). Disease etiology (Table 3) and baseline hemodynamic parameters (Table 4) were also associated with long-term survival. Of the factors analyzed, SVO_2, PVRI and a diagnosis of CHD were predictive of long-term survival. Interestingly, relative risk of death was not linear for PVRI and SVO_2. Threshold values for PVRI and SVO_2 above and below which the risk of death was greatly increased, respectively, were observed at a PVRI >30 mm Hg/liter/min/m^2 (Figure 2A) and an SVO_2 ≤55% (Figure 2B). In contrast to other studies, baseline mRAP was not found to be a significant predictor of survival in this cohort.

On-treatment predictors of survival

Of the 811 patients in the database, 12-week efficacy data, including 6MWD and hemodynamics, were available for 399 patients who had entered the long-term study after completing the blinded trials of SC treprostinil. On-treatment 6MWD did not linearly correlate with survival, but it exhibited certain threshold values for which survival

Table 4 Baseline Predictors of Survival

Prognostic factor	Hazard ratio for death (95% CI)	*p*-value
NYHA FC (vs FC III)		
II	0.79 (0.50–1.24)	<0.001
IV	2.31 (1.49–3.59)	
PVRI (mm Hg/liter/min/m^2)[a]		
>16–22	1.22 (0.66–2.28)	<0.001
>22–30	1.20 (0.66–2.19)	
>30	2.44 (1.45–4.13)	
SVO_2 (%)[b]		
>69	0.29 (0.17–0.51)	<0.001
>64–69	0.33 (0.20–0.57)	
>55–64	0.40 (0.25–0.64)	

CI, confidence interval; FC, functional class; NYHA, New York Heart Association; PVRI, pulmonary vascular resistance index; SVO_2, mixed venous oxygen saturation.

[a]Compared with reference PVRI ≤16 mm Hg/liter/min/m^2.

[b]Compared with reference SVO_2 ≤55%.

was negatively affected. A 6MWD of ≤295 m at Week 12 ($n = 391$) was associated with a marked decrease in patient survival at 3 years (Figure 3). Conversely, a ≥20-m increase from baseline to Week 12 in 6MWD was associated with higher survival rates (80%) compared with smaller walk increments (69%, $p = 0.039$). Each 20-m increase in 6MWD also correlated positively with survival ($p = 0.032$; Table 5). Hemodynamic variables were also assessed at 12 weeks after initiation of treprostinil. A PVRI ≤20 mm Hg/liter/min/m^2 was associated with an improved survival outcome ($p < 0.001$). Increases in CI of 1.0 liter/min/m^2 correlated with increased survival ($p = 0.005$). Treprostinil dose at any time-point during the 3-year study also appeared to be an important factor associated with survival. For treprostinil doses ≥40 ng/kg/min ($n = 230$ [28%]), probability of survival was significantly higher compared with lower doses ($p < 0.001$). Furthermore, every 10-ng/kg/min incremental increase in treprostinil dose was associated with improved long-term survival (Table 5). There was no statistical difference in long-term survival ($p = 0.396$) between

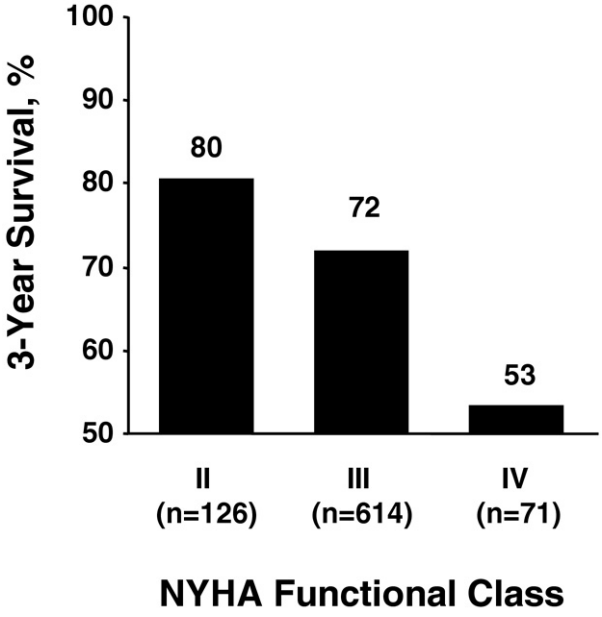

Figure 1 New York Heart Association (NYHA) functional class (FC) and 3-year survival at baseline. NYHA FC IV status was associated with a markedly lower 3-year survival rate (53%) compared with FCs III (72%) and II (80%) among patients treated with subcutaneous treprostinil.

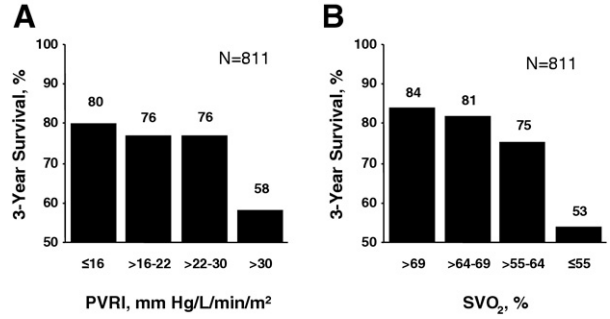

Figure 2 Baseline hemodynamic predictors of survival. (A) Pulmonary vascular resistance index (PVRI) ranges vs 3-year survival show that a PVRI >30 mm Hg/liter/min/m^2 correlated with reduced survival. (B) Mixed venous oxygen saturation (SVO_2) ≤55% correlated with reduced survival at 3 years.

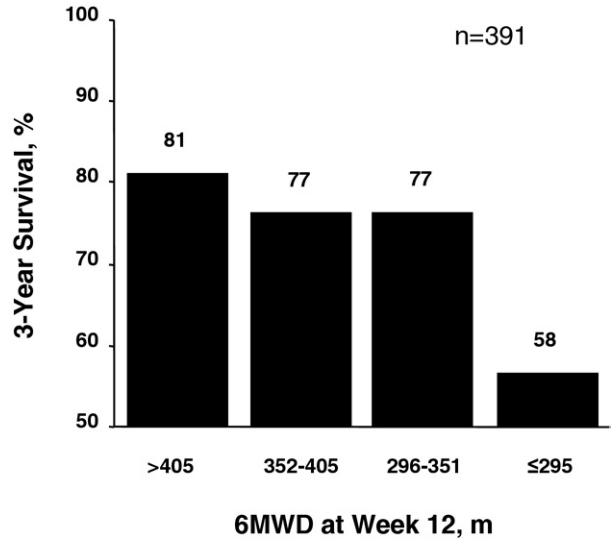

Figure 3 Exercise capacity vs survival at Week 12. A 6-minute walk distance (6MWD) ≤295 m at Week 12 strongly correlated with reduced survival at 3 years.

patients on treprostinil ($n = 190$) or placebo ($n = 209$) during the initial 12-week study.

Multivariate analyses of patient-related and on-treatment predictors of survival

Multivariate analyses were performed to ascertain the interrelationships between specific patient-related factors for baseline and on-treatment variables after 12 weeks of SC treprostinil therapy regarding prediction of long-term survival. In the univariate analyses, age, BMI, disease etiology, liver and kidney function, 6MWD, specific hemodynamic parameters and NYHA FC IV were significant baseline predictors of survival. In this analysis, the survival benefit of each factor independent of other prognostic factors was examined using a Cox proportional hazards analysis. Patient BMI ($p < 0.001$), albumin ($p < 0.001$), total bilirubin ($p = 0.033$) and creatinine ($p < 0.001$) levels were related to overall survival (Table 6). Likewise, significant individual predictors of death at 12 weeks, including 6MWD, treprostinil dose, PVRI, SVO_2 and CI, were assessed in a multivariate analysis. Only SVO_2 ($p = 0.018$), 6MWD ($p = 0.004$) and treprostinil dose ($p = 0.009$) were significant predictors of survival when analyzed in the presence of other on-treatment factors (Table 6).

Table 5 Univariate On-treatment Predictors of Survival

Prognostic factor	*n*	Hazard ratio for death (95% CI)	*p*-value
Treprostinil dose ↑ 10-ng/kg/min increments[a]	811	0.66 (0.48–0.90)	0.009
≥40 ng/kg/min[b]	230	0.29 (0.20–0.44)	<0.001
6MWD[a] ↑ 20-m increments	391	0.92 (0.86–0.99)	0.032
≥20-m increase	158	0.61 (0.38–0.98)	0.039
PVRI[a] ↓ 10 mm Hg/liter/min/m^2	335	0.70 (0.56–0.86)	<0.001
≤20 mm Hg/liter/min/m^2	354	0.40 (0.24–0.68)	<0.001
mRAP, ↑ 1 mm Hg[a]	390	1.06 (1.03–1.10)	<0.001
Cardiac index, ↑ 1 liter/min/m^{2a}	379	0.64 (0.47–0.87)	0.005

CI, confidence interval; mRAP, mean right atrial pressure; 6MWD, 6-minute walk distance; PVRI, pulmonary vascular resistance index.
[a]Measured at Week 12.
[b]Measured at any time-point during the study.

Table 6 Multivariate Predictors of Survival

Prognostic factor	Hazard ratio for death (95% CI)	*p*-value
Patient-related factors (based on available data for 811 patients)		
Age, ↑ 10 y	1.01 (0.89–1.15)	NS
BMI, ↑ 10 kg/m^2	0.52 (0.38–0.72)	<0.001
Albumin, ↑ 0.5 g/dl	0.70 (0.58–0.83)	<0.001
Sodium, ↑ 5 mmol/liter	0.90 (0.70–1.15)	NS
Total bilirubin, ↑ 0.1 mg/dl	1.02 (1.00–1.03)	0.033
Creatinine, ↑ 0.5 mg/dl	1.73 (1.31–2.28)	<0.001
On-treatment factors at Week 12		
Treprostinil dose[a] ↑ 10-ng/kg/min increments	0.64 (0.45–0.89)	0.009
6MWD[b] ↑ 20-m increments	0.86 (0.78–0.95)	0.004
PVRI[c] ↓ 10 mm Hg/liter/min/m^2	0.73 (0.44–1.21)	NS
SVO_2[d] ↑ 10% increments	0.66 (0.46–0.93)	0.018
Cardiac index[e] ↑ 1 liters/min/m^2	0.40 (0.12–1.28)	NS

BMI, body mass index; CI, confidence interval; 6MWD, 6-minute walk distance; NS, not significant; PVRI, pulmonary vascular resistance index; SVO_2, mixed venous oxygen saturation.
[a]$n = 811$; [b]$n = 391$; [c]$n = 354$; [d]$n = 365$; [e]$n = 379$.

Discussion

Because of the orphan disease status of PAH and ethical issues related to placebo treatment of patients with this debilitating disease, randomized, controlled trials are rarely adequately designed or powered to assess disease survival or prognostic factors of survival benefit.[23] In the absence of well-controlled survival trials, there is a need to identify surrogate markers to accurately predict survival. Using a large database of patients with PAH receiving SC treprostinil, we sought to identify baseline and on-treatment variables that were predictive of long-term survival.

Our findings indicate that disease etiology, kidney and liver function, NYHA FC, PVRI and SVO_2 are significant baseline predictors of survival in patients with PAH treated with SC treprostinil. It is well accepted that CTD-associated PAH has a poor prognosis. Indeed, patients with CTD were at a much higher risk of death in this study population. Similar to observations in recent studies, patients with comorbidities such as impaired renal function had a significantly worse prognosis than those with normal renal function.[19,24–26] Likewise, patients with liver dysfunction fared worse than those with normal liver function. Consistent with other reports,[8,16,19,20] NYHA FC was a strong prognostic indicator of survival in the current analysis.

Results from this analysis also reinforce the clinical benefits of optimized dosing for prostanoid use in PAH. Similar results have been seen in large, controlled trials of epoprostenol therapy, suggesting overall prostanoid use is perhaps improving PAH prognosis.[3,8,16]

Baseline hemodynamic parameters PVRI and SVO_2 were predictive of long-term survival. A PVRI >30 mm Hg/liter/min/m^2 correlated with an increased risk of death; this baseline variable was not found to be significant in other studies of PAH survival. Patients who achieved improvements in hemodynamic response to treprostinil therapy, as measured by a decrease in PVRI, had a long-term survival benefit. These results are similar to those reported by Sitbon et al[8] in which a sustained 3-month decrease in total pulmonary resistance was achieved with epoprostenol therapy. A reduced survival rate for patients with SVO_2 ≤55% was determined in the current analysis and was consistent with results from the study by Sitbon et al.[8] However, surprisingly, mRAP and mPAP were not significant baseline predictors of death in this cohort in the current analysis, in contrast to what has been reported previously.[2,8,16,20] We speculate that the lack of predictive value of mRAP in this analysis may be related to a wide standard deviation of mRAP at baseline (4.1 to 15.1 mm Hg), resulting in a lack of statistical significance. In two smaller studies, lower values for arterial oxygen saturation[18] and 6MWD[17] correlated with increased death rate. Despite encouraging data from these reports, the small patient cohort size rendered the studies inadequately powered to assess survival benefit due to variability in individual predictors.

On-treatment predictors of 3-year survival analyzed at 12 weeks included 6MWD, hemodynamics and treprostinil dose. Despite inherent flaws (such as not accounting for patient age, height and weight), the 6MWD remains the most widely used test to assess exercise capacity and risk in patients with PAH. However, a recent study has scrutinized the validity of the 6MWD as a relevant surrogate marker of survival.[14] Data from the current analysis show that long-term survival improved with a >20-m increase in 6MWD from baseline to Week 12. Moreover, for every additional 20 m walked, relative risk of death decreased, reinforcing the correlative survival benefit of improvements in walking distance. These results are important for clinicians and suggest that, for patients achieving a sub-optimal response to therapy (6MWD ≤20 m at Week 12), aggressive treatment with either a higher dose of treprostinil or additional/alternative PAH therapy may be needed to improve survival.

In this study we also identified a lower-than-expected threshold value of 6MWD associated with poor prognosis. Nearly 25% of patients in our study were on background therapy, which may imply that these patients were "sicker" than previously reported.[7] Similar studies concluded that 6MWD <380 m,[8] <332 m[17] and <165 m[19] correlated with poor survival, which represent 85-m, 37-m and 130-m differences, respectively, from the findings in the current analysis. In the current study we analyzed a much larger population of patients with PAH when compared with Miyamoto et al[17] (n = 43) and Sitbon et al[8] (n = 178), and utilized the mean change in 6MWD at Week 12 as compared with median change in distance walked, which was assessed in their studies. In addition, threshold values in our study were determined based on the distribution of the data, not by ROC curves.

Due to inherent limitations in the 6MWD[27,28] and differences in patient etiologies and their ability to perform timed tests, the lack of exercise improvement is more important than a precise inflection point by which distance walked correlates with survival. It appears that patients who walk <380 m have a poor likelihood of long-term survival, and our study implies that clinicians possibly should use an inflection point closer to 300 m in clinical practice. Taken together, irrespective of the precise inflection point for 6MWD (i.e., beyond which the risk profile changes markedly), 6MWD appears to prognosticate long-term survival in PAH.

Prostanoids remain a mainstay of therapy in PAH treatment. The prostacyclin analog, treprostinil, is recommended by the American College of Chest Physicians for treatment of high-risk patients with PAH.[1] Treprostinil therapy has been demonstrated to improve exercise capacity, FC and hemodynamics in patients with PAH.[9,21,29] Treprostinil therapy has also been shown to improve long-term survival in comparison to historic NIH registry data[21] and in the only randomized, placebo-controlled trial of prostacyclin therapy in PAH.[30] In previous studies of treprostinil, improved clinical outcomes were dependent, in part, on the dose of treprostinil therapy at 12 weeks.[7,9,30] Although the Week 12 treprostinil dose did not correlate with improved survival in this study (presumably because of sub-optimal dosing), the survival rate improved for every 10-ng/kg/min up-titration in treprostinil dose, similar to what was observed with incremental increases in 6MWD. These data should be interpreted with caution, however, as dose escalation is dependent on individual patient symptoms and the ability to tolerate higher doses of treprostinil. Nevertheless, the findings suggest that a threshold for treprostinil dosing may correlate with improved survival. Therefore, it is appealing to speculate that a dose of approximately 40 ng/kg/min may be a reasonable early target if tolerated by the patient.

Study limitations

Although the study data were analyzed from the 811-patient SC treprostinil database, on-treatment variables were only available for ≤399 patients. Moreover, patient data were

only available for those receiving SC treprostinil; no data were available for those patients who discontinued therapy. With the exception of survival, no functional or hemodynamic data were collected beyond the 12-week treatment period. The addition of concomitant PAH medications added after 12 weeks was unknown and may have altered the overall survival statistics. It is also possible that dose titrations of treprostinil may confound the analysis of long-term outcomes, as no control variable was used in these calculations. Finally, the aforementioned database of SC treprostinil could contain important variables not studied in this analysis with equal, if not greater, potential in predicting survival outcomes in PAH.

In conclusion, these data highlight the importance of accurately measuring several clinical parameters to predict long-term survival and suggest guidance to physicians regarding the relative success (or lack thereof) of current treatment strategies. In addition, early identification of patients with a poor prognosis should help physicians evaluate the relative benefits of various PAH therapies that may facilitate improved long-term survival. Further analysis of additional variables is warranted to test these hypotheses, along with evaluation of the data against other known PAH databases.

Disclosure statement

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