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Treatment of patients with pulmonary arterial hypertension at the time of death or deterioration to functional class IV: Insights from the REVEAL Registry

Harrison W. Farber, MD,[a] Dave P. Miller, MS,[b] Leslie A. Meltzer, PhD,[c] and Michael D. McGoon, MD[d]

From the [a]Pulmonary Center, Boston University School of Medicine, Boston, Massachusetts; [b]ICON Late Phase & Outcomes Research, San Francisco, California; [c]Actelion Pharmaceuticals US Inc, South San Francisco, California; and [d]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota.

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BACKGROUND: Current guidelines recommend intravenous prostacyclin as first-line therapy for patients with pulmonary arterial hypertension (PAH) in New York Heart Association/World Health Organization functional class (FC) IV, or combination therapy for patients in any FC who do not respond to monotherapy. We investigated the aggressiveness of therapy in patients enrolled in the REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) Registry who deteriorated to FC IV or died.

METHODS: Among 3,515 patients (age $\geq$ 18 years) in REVEAL with a mean pulmonary artery pressure $\geq$ 25 mm Hg and pulmonary capillary wedge pressure $\leq$ 15 mm Hg, we examined three sub-sets: the 487 patients who had a PAH-related death, the larger set of 908 patients who died from any cause (PAH-related, not PAH-related, or unknown), and the 294 patients who were FC I, II, or III at enrollment and later assessed as FC IV.

RESULTS: Among patients who died, 56% ($n = 272$ of 487) and 43% ($n = 391$ of 908) were receiving intravenous prostacyclin before death in the PAH-related death and all-cause death cohorts, respectively. In the PAH-related death cohort, 60% and 16% of patients were most recently assessed as FC III and IV, respectively; among those assessed as FC IV within 6 months of death, 57.7% ($n = 15$ of 26) had received intravenous prostacyclin. Because many patients died without an observed assessment of worsening to FC IV, we also evaluated medication use among the cohort of patients who worsened to FC IV during the study. One day before worsening to FC IV, 150 of 294 patients were not receiving intravenous prostacyclin and 70 were receiving only PAH-specific monotherapy; of these, 61% and 67%, respectively, received no additional therapy 90 days later.

CONCLUSIONS: Intravenous prostacyclin and combination therapy are not consistently used in the most seriously ill patients enrolled in REVEAL after being assessed as FC IV or at the time of death.

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Pulmonary arterial hypertension (PAH) is characterized by elevated pulmonary artery pressure (PAP) and increased pulmonary vascular resistance (PVR), frequently resulting in right ventricular dysfunction and, ultimately, right heart failure and premature death.[1–3] The clinical course of untreated PAH is progressive deterioration; historically, the prognosis for patients with untreated PAH has been very poor, with a mean survival time of 2.8 years from diagnosis.[4] Despite improved disease-specific therapeutic

Reprint requests: Harrison W. Farber, MD, The Pulmonary Center, Boston University School of Medicine, 72 E Concord St, R-304, Boston, MA 02118. Telephone: 617-638-4860. Fax: 617-536-8093.

E-mail address: hfarber@bu.edu

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options,[5–9] some patients progress, while others decline after initial improvement with medication.[1] Therefore, aggressive monitoring is critical, because patients who remain in New York Heart Association (NYHA)/World Health Organization (WHO) functional class (FC) III/IV despite therapy have poor outcomes.[1,10]

The past 2 decades have brought remarkable advances in the development of treatment options that target pathways implicated in PAH pathogenesis, namely the prostacyclin, nitric oxide, and endothelin pathways.[11,12] These agents, supported by varying degrees of evidence for their use in PAH, have been shown to improve patients' quality of life and, in some cases, survival.[13,14] Oral therapies, such as phosphodiesterase type-5 (PDE-5) inhibitors[15,16] and endothelin receptor antagonists (ERAs)[8,17] have been effective in patients with mild to moderate PAH, whereas intravenous prostacyclin is the treatment of choice for moderate to severe PAH.[7,9,18,19] Thus, current practice guidelines for the treatment of PAH propose a treatment algorithm according to the patient's risk factors.[1,10] Patients considered lower risk based on clinical assessment can initially be treated with an oral agent, whereas higher-risk patients, including those with NYHA/WHO FC IV, should receive intravenous prostacyclin.[1,10]

Although many patients with PAH benefit from these available drug therapies, a sub-set of patients experience minimal to no improvement after therapy is initiated, and others may experience clinical deterioration after initial improvement.[20] As such, several studies have suggested that combining agents that exert their effects on different, yet complementary, pathophysiologic pathways may provide an additive or synergistic effect and improved outcome in patients unsuccessfully managed with a single agent. Although limited by sample size and lack of long-term observations, several studies have shown the effectiveness and safety of different combination therapies.[21–26] This evidence and the chronic and progressive nature of PAH provide the rationale for current guideline recommendations regarding the initiation of combination therapy in patients in any FC who do not respond adequately to monotherapy and optimized background treatment. The guidelines also recommend that patients be reassessed every 3 to 6 months and a new therapy added when treatment goals have not been met.[1,10]

The REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) Registry is the largest multicenter, observational United States-based registry of patients with PAH established to date.[27,28] REVEAL was designed to provide current information on demographics, course, and management of patients with group 1 PAH. A primary objective of REVEAL is to characterize the clinical features and outcomes of patients with PAH currently under care at PAH centers.[27,28] To gain insight into the aggressiveness of therapy and adherence to guideline recommendations for the treatment of patients in REVEAL with the most severe disease, we investigated PAH-specific therapy at time of death and at the time of and after clinical worsening to NYHA/WHO FC IV.

Methods

Study design

Study design and baseline characteristics of patients enrolled in REVEAL have been described previously.[27,28] Briefly, REVEAL is a 55-center (university-affiliated and community hospitals) observational, United States-based study.[29] Patients are monitored for 5 years from the time of enrollment. Each participating center obtained Institutional Review Board approval before patient enrollment, and all patients provided informed consent. "Enrollment" was defined as the date consent was given.

Study population

REVEAL inclusion criteria consist of newly (diagnostic right heart catheterization $\leq$ 3 months of enrollment) and previously (diagnostic right heart catheterization $\geq$ 3 months before enrollment) diagnosed patients with group 1 PAH at the time of enrollment.[30] Hemodynamic parameters confirming PAH included mean PAP (mPAP) $\geq$ 25 mm Hg at rest or left ventricular end-diastolic pressure (LVEDP) $\leq$ 18 mm Hg, and PVR $\geq$ 240 dynes • sec • cm^{-5}. REVEAL uses a less restrictive pulmonary capillary wedge pressure (PCWP) criterion of $\leq$ 18 mm Hg to be more inclusive of patients seen in real-world clinical practice.[27,28,31] Excluded from current analyses were patients who were aged $\leq$ 17 years at enrollment, met the mPAP entry criteria during exercise, and had a PCWP of 16 to 18 mm Hg at diagnosis, who underwent transplantation or atrial septostomy, or who were participating in a blinded clinical trial at the last follow-up before death (Figure 1). REVEAL was initiated before the issuance of the Fourth World Symposium on PAH and conforms to the etiology sub-group classifications issued by the Third World Symposium on Pulmonary Hypertension.[29]

Analysis design

Medications were categorized into 12 possible combinations of the following: PDE-5 inhibitors, ERAs, prostacyclin subdivided into parenteral (intravenous/subcutaneous) and non-parenteral (inhaled/oral), including a category for "none." Treatment was investigated at the first assessment of worsening to NYHA/WHO FC IV; at 90 days, 30 days, and 1 day before worsening assessment; and at 30 and 90 days after worsening assessment. Treatment was also investigated at the time of death. Sub-sets of patients in FC III and FC IV who had recent FC assessments (within 6 months before death) were evaluated separately to rule out treatment decisions that had been based on patients who had not had a recent evaluation or who were not in a high-risk group by FC alone.

Statistical analysis

This is a descriptive analysis and does not assess a specific hypothesis. Although it is not expected that the guidelines would be followed for 100% of patients, it requires only 1 patient for whom guidelines are not followed to disprove that they are monitored 100% of the time. As such, no formal statistical tests were conducted. Continuous data are summarized as means $\pm$ standard deviations, and categoric data are summarized as percentages where the denominator is the count of patients with non-missing data for a given variable. Analyses summarizing the distribution of medication regimens before death were repeated for the sub-set of deaths categorized as PAH-related.

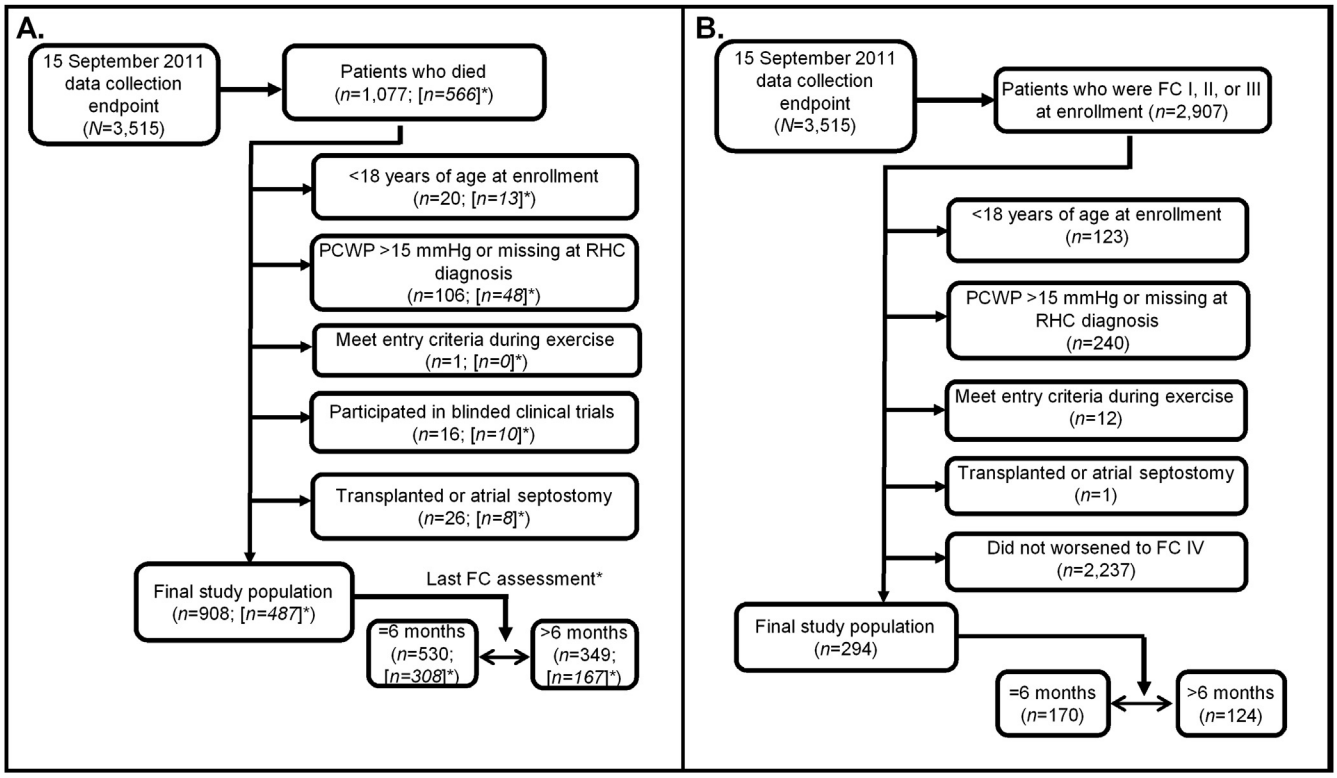

Figure 1 Study design. An enrollment algorithm for the three analyses is shown, designed to ensure that all patients included in this analysis met the criteria set forth. (A) The design for the all-cause death cohort and pulmonary arterial hypertension (PAH)-related death cohort is shown. (B) Design for the cohort with worsening functional class (FC) is shown. Excluded from analyses were patients who were aged < 18 years at enrollment, had a pulmonary capillary wedge pressure (PCWP) of 16 to 18 mm Hg at diagnosis, met REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) hemodynamic entry criteria during exercise, who received a transplantation or an atrial septostomy, or who were participating in a blinded clinical trial at last follow-up. RHC, right heart catheterization. *Indicates PAH-related death cohort analysis.

Results

Patient characteristics

At the data collection end point on September 15, 2011, 3,515 adult (aged ≥18 years) patients with PAH had been enrolled in REVEAL. Of these, 29% were newly diagnosed and 71% were previously diagnosed. Demographic characteristics of the PAH-related death, all-cause death, and FC worsening cohorts are reported in Table 1.

PAH-related death cohort

Inclusion criteria and demographic characteristics for the PAH-related death cohort ($n = 487$; 73% female) are shown in Figure 1A and summarized in Table 1, respectively. Patients were a mean age at enrollment of 56.3 ± 14.5 years. At enrollment, 43% of patients were diagnosed with idiopathic PAH (IPAH), and the next largest sub-group, at 33%, was patients with PAH associated with connective tissue disease (CTD; Table 1).

Analysis of the PAH-related death cohort based on time of the last FC assessment revealed similar characteristics for patients whose last FC assessment was ≤ 6 months vs > 6 months before PAH-related death; however, compared with patients in the > 6-month group, patients in the ≤ 6-month group had a slightly decreased incidence of IPAH (48% vs 42%), obesity (35% vs 27%), and diabetes (21% vs 15%), and slightly more CTD (28% vs 36%), respectively (Table 2).

All-cause death cohort

Among 1,077 patients who died, 908 met all of the inclusion criteria for this analysis and represented the final study population in the all-cause death cohort (Figure 1A). Demographic characteristics of these patients were similar to those reported for the PAH-related death cohort and are summarized in Table 1 (column A).

FC worsening cohort

At study entry, 2,907 patients were FC I, II, or III. Of these, 294 patients (77% female) were subsequently classified as FC IV and were defined as the FC worsening cohort (Figure 1B). These patients were a mean age of 55 ± 14.4 years at enrollment. Consistent with the all-cause death cohort, patients with IPAH (47%) and CTD (31%) were the largest groups in this cohort. Newly and previously diagnosed patients represented 23% and 77% of the cohort, respectively (Table 1, column B).

Medication use at time of death

Analysis of PAH-specific medications that patients were receiving before death in the all-cause death cohort and

Table 1 Demographic Characteristics of Patients Who Died During the REVEAL Assessment Period or Worsened to New York Heart Association/World Health Organization Functional Class IV

Characteristic	PAH-related death ($n = 487$)	All-cause death ($n = 908$)	FC worsening ($n = 294$)
Age at enrollment, mean ± SD years	56.3 ± 14.5	57.5 ± 14.4	55.0 ± 14.4
Female, *n* (%)	357 (73.3)	666 (73.3)	227 (77.2)
Group I PH sub-group at enrollment, *n* (%)			
Idiopathic PAH	211 (43.3)	363 (40.0)	138 (46.9)
Associated with PAH			
Congenital heart disease	47 (9.7)	70 (7.7)	22 (7.5)
CVD/CTD	162 (33.3)	309 (34.0)	91 (31.0)
Drugs and toxins	15 (3.1)	31 (3.4)	20 (6.8)
Human immunodeficiency virus	4 (0.8)	13 (1.4)	2 (0.7)
Porto-PH	30 (6.2)	84 (9.3)	11 (3.7)
Other	3 (0.6)	8 (0.9)	1 (0.3)
Familial PAH	14 (2.9)	23 (2.5)	7 (2.4)
Peripheral vascular disease	1 (0.2)	7 (0.8)	2 (0.7)
Newly diagnosed, *n* (%)	131 (26.9)	260 (28.6)	67 (22.8)
Time on study before event, *n*	487	908	294
Mean ± SD days	624.9 ± 453.3	643.9 ± 462.9	528.2 ± 421.1
6MWD at enrollment, *n*	356	667	243
Mean ± SD m	297.8 ± 128.3	296.1 ± 125.8	310.3 ± 117.8
Mean PAP at RHC diagnosis, *n*	487	908	293
Mean ± SD mm Hg	51.3 ± 13.3	50.6 ± 12.8	50.5 ± 12.7
PAOP at RHC diagnosis, *n*	487	908	293
Mean ± SD mm Hg	9.3 ± 3.5	9.4 ± 3.5	9.5 ± 3.4
Mean RAP at RHC diagnosis, *n*	454	835	273
Mean ± SD mm Hg	10.4 ± 6.2	10.1 ± 6.0	10.3 ± 5.9
PVR at RHC diagnosis, *n*	467	878	285
Mean ± SD Wood units	12.0 ± 7.9	11.4 ± 7.0	11.7 ± 8.4
Cardiac index at RHC diagnosis, *n*	355	666	207
Mean ± SD liters/min/m^2	2.2 ± 0.8	2.3 ± 0.8	2.2 ± 0.8

6MWD, 6-minute walk distance; CVD/CTD, collagen vascular disease/connective tissue disease; FC, functional class; PAP, pulmonary artery pressure; PAH, pulmonary arterial hypertension; PAOP, pulmonary artery occlusion pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right arterial pressure; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; RHC, right heart catheterization; SD, standard deviation.

PAH-related death cohort is shown in Figures 2A and B, respectively.

PAH-related death cohort

Among the 487 patients who had a PAH-related death during the study period, 272 (55.9%) were receiving intravenous prostacyclin as monotherapy or combination therapy before death, 317 (65.1%) were receiving combination therapy, and 28 (5.7%) were receiving no therapy. At time of death, most patients were assessed as FC III or IV, with a similar proportion of patients in both classes. Among the 308 patients whose FC was assessed within 6 months of death, 135 (43.8%) were FC IV and 136 (44.2%) were FC III, whereas 1 (0.3%) was FC I and 36 (11.7%) were FC II. The mean time between the last FC assessment and death was 1.52 ± 1.57 months (median, 0.95 months) in the FC IV group and 2.36 ±1.60 months (median, 2.09 months) in the FC III group. In the FC IV group, 32.6% of patients ($n = 44$ of 135) were not receiving intravenous prostacyclin at time of death, including nearly 4% who were receiving no medication (Figure 3B).

A total of 36.8% ($n = 179$ of 487) patients died without FC assessment within 6 months of death. Among 167 of these patients, 1.2% ($n = 2$) were FC I, 23.4% ($n =39$) were FC II, 59.9% ($n = 100$) were FC III, and 15.6% ($n = 26$) were FC IV at the time of their last FC assessment. Of these patients, 12 did not have an FC assessment at any time. Only 57.7% ($n = 15$ of 26) of the FC IV patients received intravenous or subcutaneous prostacyclin before death.

All-cause death cohort

Considering all deaths, regardless of cause, 908 patients died during the study period; 392 (43%) were receiving intravenous prostacyclin as monotherapy or combination therapy before death, 520 (57%) were receiving combination therapy, and 69 (8%) were receiving no therapy. At the time of death, most patients had been most recently assessed as FC III. A sensitivity analysis, focusing on FC III and IV patients and excluding patients who had not had a recent FC evaluation, was performed to determine if the percentage was similar. Among the 530 patients whose FC was assessed within 6 months of death, 259 (49%) were FC III and 192 (36%) were FC IV, whereas 3 (0.6%) were FC I and 76 (14.4%) were FC II. The mean time between the last FC assessment and death was 2.42 ± 1.70

Table 2 Demographic Characteristics for Patients in the Pulmonary Arterial Hypertension-Related Death Cohort

	Last FC assessment[a]	
	≤ 6 months	> 6 months
Characteristic	(n = 308)	(n = 167)
Age at enrollment, mean ± SD years	56.4 ± 14.4	56.0 ± 14.6
Female, n (%)	229 (74.4)	118 (70.7)
Group I PH sub-group at enrollment, n (%)		
Idiopathic PAH	129 (41.9)	80 (47.9)
Associated with PAH		
Congenital heart disease	31 (10.1)	14 (8.4)
Connective tissue disease	112 (36.4)	47 (28.1)
Porto-PH	16 (5.2)	12 (7.2)
Drugs and toxins	7 (2.3)	7 (4.2)
Human immunodeficiency virus	2 (0.6)	1 (0.6)
Other	2 (0.6)	1 (0.6)
Familial PAH	8 (2.6)	5 (3.0)
Pulmonary venoocclusive disease	1 (0.3)	0 (0.0)
Comorbid conditions, n (%)		
Obesity[b]	75 (26.5)	54 (35.3)
Sleep apnea	49 (17.4)	41 (26.3)
Thyroid disease[c]	74 (24.6)	35 (21.3)
Hypertension[d]	120 (39.9)	69 (42.1)
Clinical depression[e]	77 (25.6)	44 (26.8)
Diabetes	44 (14.6)	35 (21.3)
COPD	42 (14.0)	29 (17.7)

COPD, chronic obstructive pulmonary disease; FC, functional class; PAH, pulmonary arterial hypertension; SD, standard deviation.

[a]12 patients did not have a functional class assessment.

[b]Obesity is defined as body mass index ≥ 30 kg/m^2 using the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: Evidence Report. National Heart, Lung and Blood Institute, June 1998.

[c]Thyroid disease is defined as patients with hyperthyroidism or hypothyroidism and/or patients having taken synthetic thyroid replacement for hypothyroidism.

[d]Hypertension includes patients with the comorbid condition hypertension and/or patients with a reported use of β blockers as a concomitant medication.

[e]Clinical depression includes patients with the comorbid condition clinical depression and/or patients with the reported use of selective serotonin reuptake inhibitors as a concomitant medication.

months (median, 2.17 months) in the FC III group and 1.68 ± 1.62 months (median, 1.12 months) in the FC IV group. In the FC IV group, 41% of patients (n = 79 of 192) were not receiving intravenous prostacyclin at time of death, including nearly 5% who were receiving no treatment (Figure 3A).

A total of 41% (n = 378 of 908) of patients died without FC assessment within 6 months of death. Among 349 of these patients, 1.4% (n = 5) were FC I, 26% (n = 91) were FC II, 59.3% (n = 207) were FC III, and 13.2% (n = 46) were FC IV at the time of their last FC assessment. Of these patients, 29 did not have an FC assessment at any time. Only 50% (n = 23 of 46) of the FC IV patients received intravenous or subcutaneous prostacyclin before death.

Medication use at time of worsening to NYHA/WHO FC IV

Given the finding that many patients did not have an FC assessment within 6 months of death, we hypothesized that if physicians were more proactive about assessing FC, patients would be more likely to receive intravenous prostacyclin and/or combination therapy when they need it most. If this were the case, we would expect a significant shift toward the use of intravenous prostacyclin and/or combination therapy in patients who were recently assessed as having worsened to FC IV. To investigate this hypothesis, we evaluated medication use at 90 days, 30 days, and 1 day before the assessment of worsening FC, and at 30 and 90 days after this assessment. Among the overall cohort who deteriorated to FC IV, 144 patients (49%) were receiving monotherapy (n = 17) or combination therapy (n = 127) that included intravenous prostacyclin 1 day before the assessment of worsening. Thus, 1 day before worsening to FC IV, 150 of 294 patients were not receiving intravenous prostacyclin and 70 were receiving only PAH-specific monotherapy. Of these, 61% and 67%, respectively, received no additional therapy 90 days later. At 30 and 90 days after worsening assessment, 51% and 52% of surviving patients, respectively, were receiving intravenous prostacyclin.

Discussion

These observations from REVEAL demonstrate that, despite current guideline recommendations, a substantial number of patients were not being treated as aggressively as guidelines suggest with intravenous prostacyclin and/or combination therapy at time of death and before or after being assessed as worsening to FC IV. A substantial number of patients were receiving only monotherapy at time of PAH-related death, and only 56% were receiving intravenous prostacyclin. The age-adjusted estimated mortality rate for the general United States population is 0.8%,[32] so many deaths may be PAH-attributable even if they are not directly PAH-related. Among all-cause deaths, only 43% were receiving intravenous prostacyclins.

In addition to more aggressive treatment to prevent clinical decline in patients with FC III and IV PAH, current guidelines recommend that these patients be monitored more frequently. Yet, results from our analyses demonstrate that, at time of death, most patients were most recently assessed as FC III. We theorized that patients would be more likely to receive intravenous prostacyclin and/or combination therapy if physicians were more proactive about assessing FC; however, this proved to be incorrect.

These findings raise concerns that substantial gaps still exist in the management of patients with more advanced disease: intravenous prostacyclin and combination therapy are not consistently used in patients with FC III/IV PAH.

Several explanations may be offered for the apparent lack of guideline adherence. Clinicians may not be sufficiently aware of the severity or progression of disease because patient follow-up is too infrequent to assess disease progression or because

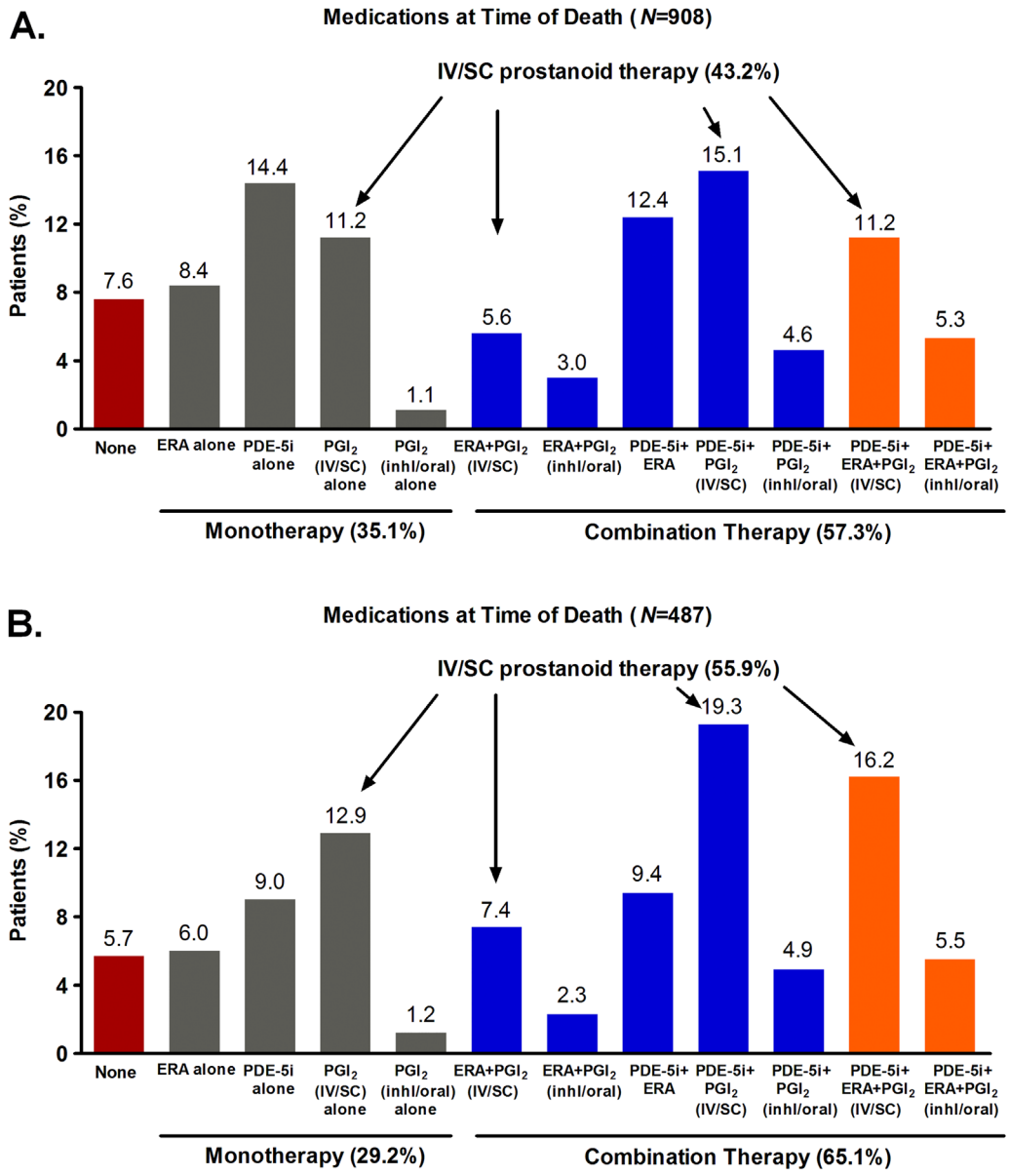

Figure 2 Medication use at time of death—overall. Pulmonary arterial hypertension (PAH)-specific therapy at time of death in (A) the all-cause death cohort ($n = 908$) and (B) the PAH-related death cohort ($n = 487$). The percentages of patients taking monotherapy plus those receiving no therapy almost total the percentage of patients taking prostanoid therapy in the all-cause death cohort, whereas a comparatively greater percentage of patients were taking prostanoid therapy in the PAH-related death cohort. Red, no therapy; grey, monotherapy; blue, dual therapy; and orange, triple therapy. ERA, endothelin receptor antagonist; inh, inhaled; IV/SC, intravenous/subcutaneous; PDE-5i, phosphodiesterase type-5 inhibitor; PGI_2, prostacyclin.

clinicians are not attaching enough significance to indicators of poor prognosis. Another explanation may be that patients and/or clinicians are unwilling or unable to apply complex therapy or that they do not believe that intravenous prostacyclin is more efficacious than other drugs at late stages of disease. Physicians may also make a conscious decision to avoid "heroic" therapy in some patients, such as elderly patients, patients with comorbid diseases, or patients seeking comfort care only. Lack of patient acceptance, lack of referral, and physician bias, especially when discussing options with the patient, may all be other explanations. Alternatively, appropriate therapy may have been attempted but was stopped due to lack of tolerance or efficacy or the patient's lack of medical coverage. Indeed, our data indicate that 65 of the patients who were not receiving an intravenous prostacyclin at time of death had previously received intravenous therapy but stopped before death.

Prostacyclins are well-established across guidelines as the gold standard of treatment for PAH and "rescue therapy" for the deteriorating patient.[33] Because of the very high short-term mortality in patients with FC IV PAH, it has become standard practice to use the most potent therapy available in this population.[33] Numerous clinical studies have investigated the potential benefits of continuous intravenous prostacyclin (epoprostenol) and, although limited by the relatively small number of patients enrolled, have all shown a dramatic effect of this treatment in patients with moderate to severe PAH[9] or in patients with moderate to severe PAH secondary to scleroderma.[19] Furthermore,

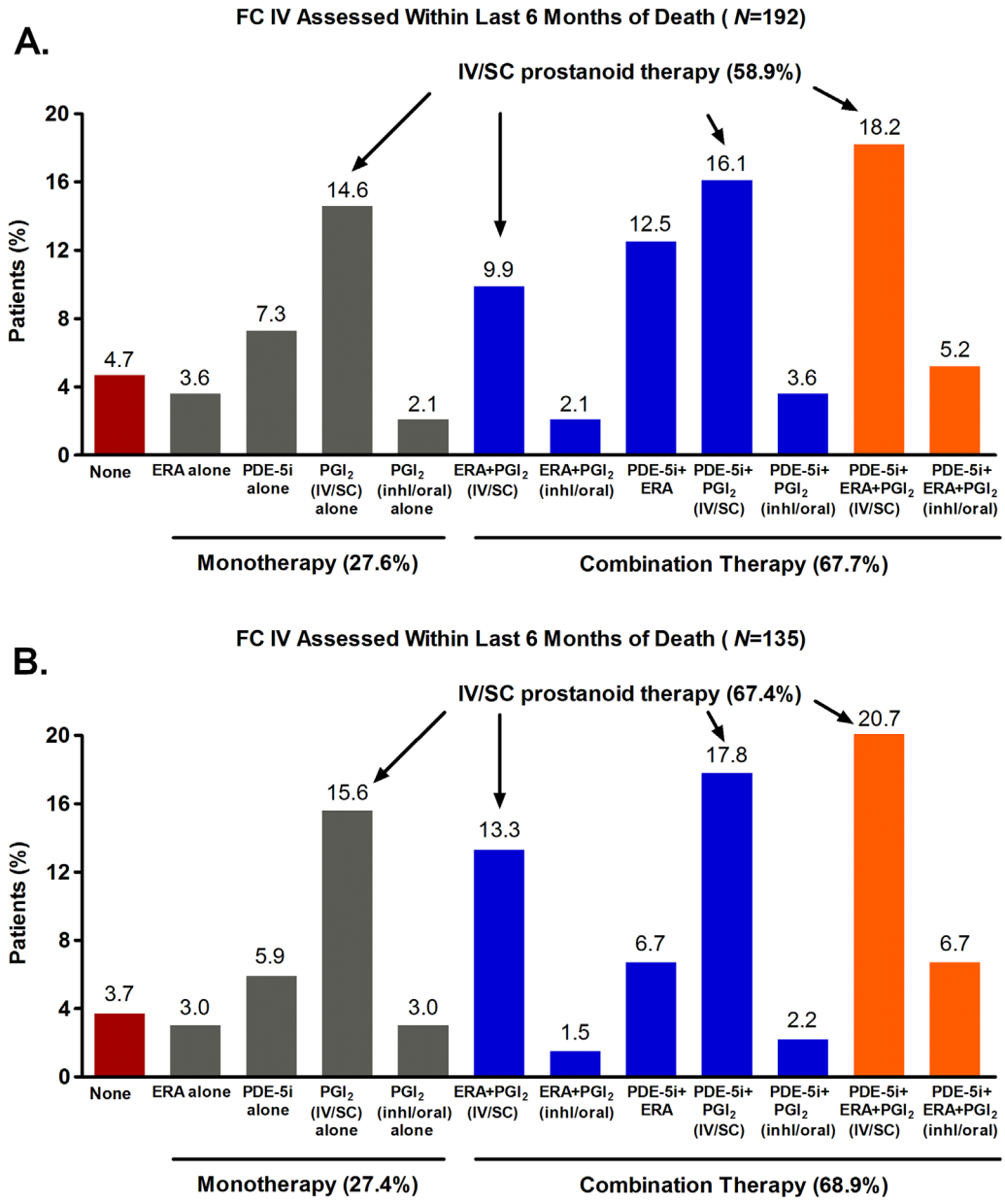

Figure 3 Medication use in patients with functional class (FC) IV assessed within the last 6 months before death. Pulmonary arterial hypertension (PAH)-specific therapy in patients who had an FC assessment within the last 6 months before death (A) in the all-cause death cohort ($n = 192$) and (B) in the PAH-related death cohort ($n = 135$). Excluded from analyses were patients who were aged $\leq$ 17 years at enrollment, had a pulmonary capillary wedge pressure of 16 to 18 mm Hg at diagnosis, met REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) hemodynamic entry criteria during exercise, received a transplantation or an atrial septostomy, or were participating in a blinded clinical trial at last follow-up before death. Red, no therapy; grey, monotherapy; blue, dual therapy; and orange, triple therapy. ERA, endothelin receptor antagonist; inh, inhaled; IV/SC, intravenous/subcutaneous; PDE-5i, phosphodiesterase type-5 inhibitor; PGI_2, prostacyclin.

significant improvements in survival have been reported with long-term continuous intravenous prostacyclin therapy compared with historical controls.[13,34,35]

Prostacyclins also play an important role in combination therapy, such as when a patient's condition has deteriorated after monotherapy with other agents.[36] Although most studies are limited by the relatively small numbers of patients enrolled, addition of agents with different mechanisms of action or alternate delivery routes has suggested improvement in exercise capacity, FC, hemodynamic measurements, and time to clinical worsening.[21,22,24,37–39]

This study has some limitations. The primary limitation of these analyses is that we evaluated medication use knowing which patients died. At the time a treatment decision is made, it cannot be known who will die, who will live, and who will benefit most from a change in therapy. Thus, this cannot be an analysis of efficacy but rather is an analysis in which the efficacy of certain therapies is presumed based on prior clinical trials and guideline recommendations.

In addition, deterioration can occur quickly in PAH; therefore, we do not know whether there was a plan for

some patients to begin therapy soon at the time of their death. We only know that they were not on therapy at time of death. Furthermore, we do not have any information on the reasons that medications were not administered, including past treatment failures on prostacyclins. Also of importance, we cannot know with certainty the respective roles of physicians and patients in these therapeutic decisions or what role, if any, insurance coverage could have played in the decisions. These are all areas of intense interest with potentially important clinical implications; further information and investigations concerning these observations are warranted.

In conclusion, despite guideline recommendations regarding the treatment of patients with PAH with the most severe disease, and despite the body of evidence regarding benefits of intravenous prostacyclin and/or combination therapy in these patients, intravenous prostacyclin and combination therapy are not consistently used in patients enrolled in REVEAL at the time of or after FC IV assessment. Importantly, intravenous prostacyclin therapy is not frequently used in patients with FC IV PAH before their death.

Disclosure statement

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David Badesch, MD, University of Colorado Health Sciences Center, Aurora, CO, and Deb McCollister, RN; Erika Berman-Rosenzweig, MD, Columbia University, New York, NY, and Daniela Brady, RN; Charles Burger, MD, Mayo Clinic, Jacksonville, FL, and Pamela Long, RN, CCRP; Sif Hansdottir, MD, University of Iowa Hospitals & Clinics, Iowa City, IA, and Page Scovel, RN, BSN; Murali Chakinala, MD, FCCP, Washington University, St. Louis, MO, and Ellen Lovato, RN, BSN; Monica Colvin-Adams, MD, University of Minnesota Medical Center, Fairview, Minneapolis, MN, and Nonyelum Harcourt; Maria Rosa Costanzo, MD, Midwest Heart Foundation, Naperville, IL, and Debbie Heidenreich, RN, BSN; Curt Daniels, MD, Children's Research Institute at Ohio State, Columbus, OH, and Julianne Williamson-Mueller, RN, BSN; Curt Daniels, MD, Ohio State University, Columbus, OH, and Jami Maccombs; Raed Dweik, MD, Cleveland Clinic Foundation, Cleveland, OH, and Jennie Newman; Greg Elliott, MD, Intermountain Medical Center and the University of Utah, Salt Lake City, UT, and Natalie Kitterman, RN, BSN; CCRP, Harrison Farber, MD, Boston University School of Medicine, Boston, MA, and Kim Tobin Finch; Robert Frantz, MD, Mayo Clinic College of Medicine, Rochester, MN, and Louise Durst, RN; Adaani Frost, MD, Baylor College of Medicine, Houston, TX, and Helena Purl, RN, BSN; Mardi Gomberg, MD, University of Chicago Hospitals, Chicago, IL, and Sandra Coslet, RN, MSN, MBA; James Gossage, MD, Medical College of Georgia, Augusta, GA, and Melissa James, RN; Dan Grinnan, MD, Virginia Commonwealth University, Richmond, VA, and Amy Frayser; Paul Hassoun, MD, Johns Hopkins Medical Center, Baltimore, MD, and Jude Aidam, MB, ChB, MPH, CM, CCRP; Kristin Highland, MD, Medical University of South Carolina, Charleston, SC, and Laura Bailey; Nicholas Hill, MD, Tufts-New England Medical Center, Boston, MA, and Karen Visnaw, RN; Dunbar Ivy, MD, Children's Hospital Department of Cardiology, Aurora, CO, and Kathleen Miller-Reed, RN; James Klinger, MD, Rhode Island Hospital, Providence, RI, and Barbara Smithson, RN, BSN; Steve Knoper, MD, University of Arizona, Tucson, AZ; Deborah Jo Levine, MD, University of Texas Health Science Center, San Antonio, TX, and Regina Whitener, RN, BSN; George Mallory, MD, Texas Children's Hospital, Houston, TX, and Ann Bogran, RN, BSN; Catherine Markin, MD, Legacy Clinic Northwest, Portland, OR, and Lisa Roessel, RN, FNP, ARNP-BC; Michael Mathier, MD, University of Pittsburgh School of Medicine, Pittsburgh, PA, and Mary Pollera, RN; Wesley McConnell, MD, Kentuckiana Pulmonary Associates, Louisville, KY, and Kim Hobbs, MSN, ARNP; Dana McGlothlin, MD, UCSF Medical Center, San Francisco, CA, and Erin Kobashigawa, BA; Donald Moore, MD, Children's Hospital at Vanderbilt, Nashville, TN, and Mary Beth Boyd, RN, BSN; Hassan Alnuaimat, MD, MD, University of Florida, Gainesville, FL, and Christina Eagan; Srinivas Murali, MD, Allegheny General Hospital, Pittsburgh, PA, and Pranav Ravi, MBBS; Steven Nathan, MD, Inova Heart and Vascular Institute, Falls Church, VA, and Lori Schlegel, RN, BSN; Ronald Oudiz, MD, LA Biomedical Research Institute at Harbor-UCLA, Torrance, CA, and Joy Beckman, RN, MSN; Myung Park, MD, University of Maryland School of Medicine, Baltimore, MD, and Faith E. Pa'ahana-Janowick, RN, BSN; Ivan Robbins, MD, Vanderbilt University Medical Center, Nashville, TN, and Tracy Oyler, RN; David Ross, MD, UCLA Medical Center, Los Angeles, CA, and Michaela Dyke; Ghulam Saydain, MD, FCCP, Wayne State University, Detroit, MI, and Muhammad Usman, MD; Robert Schilz, DO, PhD, University Hospital of Cleveland, Cleveland, OH, and Dave Haney, RRT; Shelley Shapiro, MD, PhD, VA Greater Los Angeles Health System, Los Angeles, CA, and Wendy Hill, RN, NP, MSN; Roxana Sulica, MD, Beth Israel Medical Center, New York, NY, and Rebecca Fenton, RN; John Swisher, MD, Suncoast Lung Center, Sarasota, FL, and Laura Karasick; Darren Taichman, MD, PhD, University of Pennsylvania Medical Center, Philadelphia, PA, and Mamta J. Patel, RN, BSN; Jose Tallaj, MD, University of Alabama at Birmingham, Birmingham, AL, and Terri Tahmaseb, RN; Arunabh Talwar, MD, North Shore University-LIJ Medical Center, New Hyde Park, NY, and Rebecca Miller; Victor Tapson, MD, Duke University Medical Center, Durham, NC, and Sandy McNeilly; Victor Test, MD, UCSD Medical Center, La Jolla, CA, and Melissa Thrasher, CCRC; Ramagopal Tumuluri, MD, St. Luke's Medical Center- Aurora, Milwaukee, WI, and Susan Oxborough, RN, CVN; Hector Ventura, MD, Ochsner Clinic Foundation, New Orleans, LA, and Bobbett Harris; Aaron Waxman,

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