A Review of Clinical Trial Endpoints of Patients with Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension and How They Relate to Patient Outcomes in the United States

Christine Divers, PhD; David Platt, MD; Edward Wang, PharmD, MBA; Jay Lin, PhD, MBA; Melissa Lingohr-Smith, PhD; and Stephen C. Mathai, MD, MHS

SUMMARY

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are subgroups of pulmonary hypertension and are considered rare diseases. Understanding how endpoints of clinical trials (and patient registry studies) of patients with PAH and CTEPH are associated with patient outcomes is important in order to address the concerns of patients, health care providers, decision makers, and payers. The purpose of this review was to examine how endpoints used in clinical trials and patient registry studies are associated with outcomes of patients with PAH and CTEPH.

A PubMed literature search was conducted to retrieve published studies, including randomized phase III clinical trials and observational studies, from years 2000 to May 2015 that evaluated the associations between change in 6-minute walking distance (6MWD), 6MWD thresholds, change in World Health Organization functional class (WHO-FC), and time to clinical worsening with outcomes of patients with PAH and CTEPH.

Based on this review of published literature, a reduction in 6MWD as a criterion for PAH worsening, a deterioration in WHO-FC, and delay in the time to clinical worsening are clinically meaningful trial endpoints and are associated with outcomes of patients with PAH and CTEPH. Utilization and standardization of these endpoints will be useful for comparing interventions of clinical trials and therapies. Hospitalizations are frequent among patients with PAH and CTEPH, and total health care costs are high. From a U.S. payer perspective, clinical worsening is an important composite endpoint in that it includes hospitalization, which can be transformed into a preventative cost value associated with efficacious treatment of patients with PAH and CTEPH. In view of the greater number of medications available to treat PAH, the introduction of the first approved therapy to treat CTEPH, and the increasing use of combination pharmacotherapy, reliable prognostic markers of treatment responsiveness are important to help guide appropriate management. As new clinical trials and observational studies are conducted, it will be important to maintain universal endpoints so that health care providers, decision makers, and payers can better understand the value of targeted pharmacotherapies and combination therapies for the treatment of patients with PAH and CTEPH.

J Manag Care Spec Pharm. 2017;23(1):92-104

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What is already known about this subject

- Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are rare diseases associated with significant morbidity and high mortality.
- Some studies have found that the health care and economic burdens of patients with PAH and CTEPH are substantial, although because of the lack of specific coding for these rare diseases, there is a level of uncertainty regarding the true burden of PAH and CTEPH.
- In view of the greater number of medications available to treat PAH and the introduction of the first approved therapy to treat CTEPH, reliable prognostic markers of treatment responsiveness are important to help guide appropriate management.

What this study adds

- This review describes the endpoints of clinical trials and observational studies of patients with PAH and CTEPH and how they relate to patient outcomes.
- Based on this review of published literature, a reduction in 6-minute walking distance as a criterion for PAH worsening, a deterioration in World Health Organization functional class, and delay in the time to clinical worsening are clinically meaningful trial endpoints and are associated with outcomes of patients with PAH and CTEPH.
- As new clinical trials and studies of patient registries are conducted, it will be important to maintain universal endpoints so that health care providers, decision makers, and payers can better understand the value of new targeted pharmacotherapies and combination therapies for the treatment of patients with PAH and CTEPH.

Pulmonary arterial hypertension (PAH) is a progressive disease resulting from restricted flow through the pulmonary arteries and leading to increased pulmonary vascular resistance and ultimately right heart failure and death.¹ Chronic thromboembolic pulmonary hypertension (CTEPH) is similar to PAH but is caused by obstruction of the

pulmonary arteries with intraluminal organized thrombus.² PAH and CTEPH are subgroups of pulmonary hypertension (PH) and are considered rare diseases.^{1,2} In the United States, the prevalence of PAH per 1 million individuals is estimated at 109 among persons aged <65 years and at 451 among persons aged ≥65 years.³ The prevalence of CTEPH per 1 million individuals is estimated at 63 among persons aged <65 years and at 1,007 among persons aged ≥65 years.³ Other studies conducted in Europe have reported lower prevalence of PAH and CTEPH.^{4,5} Using registry data from France, the prevalence of PAH was reported as 15-25 cases per million adults.⁴ Based on a registry in Spain, the prevalence of CTEPH was reported as 3.2 cases per million adults.⁵ The true prevalence of PAH and CTEPH is difficult to gauge, since both lack specific diagnostic coding to distinguish from other types of PH and are frequently underdiagnosed and/or misdiagnosed.^{6,7} The prognosis of either PAH or CTEPH is poor.^{1,2} The 1-, 3-, 5-, and 7-year survival rates of patients with PAH were estimated at 85%, 68%, 57%, and 49%, respectively, based on the U.S. Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL Registry) study.⁸ Among patients with inoperable CTEPH, the 1- and 3-year survival rates were estimated at 82% and 70%, respectively, based on a study in the United Kingdom.⁹

The pathogenesis of PAH is predominately related to loss of vascular luminal cross section resulting from vascular tissue remodeling, with excessive vasoconstriction also contributing in approximately 20% of patients.¹ CTEPH arises from emboli, which become fibrotic scar tissue that progressively causes microvascular lesions and vascular remodeling.¹ CTEPH can occur as a complication (2%-4% cumulative incidence) after pulmonary embolism (PE); however, many CTEPH patients have no history of PE.^{1,10,11} Hemodynamically, PAH and CTEPH are defined by a mean pulmonary artery pressure (PAP) ≥25 mmHg at rest, a pulmonary artery wedge pressure ≤15 mmHg, and a pulmonary vascular resistance (PVR) >3 Wood units.^{1,11,12} The main symptom of PAH and CTEPH is dyspnea.¹ Other symptoms of PAH and CTEPH include fatigue, weakness, and syncope.^{1,2,11} The vague symptomatology of PAH and CTEPH leads to diagnoses made most commonly at late stages of the diseases.⁷ Data from the REVEAL and French national registries indicate that 72% and 75% of patients with PAH when diagnosed are classified at World Health Organization functional class (WHO-FC) III and IV, respectively, indicating marked limitation of physical activity.^{4,7,13}

Treatment of Patients with PAH

Until the 1990s, PAH was managed with support treatments directed against symptoms, which included anticoagulation

therapy, diuretics, oxygen, and digoxin.¹⁴ Over the past 20 years, advances in our understanding of the pathogenesis of the disease have led to development of targeted therapeutics for PAH. Currently, there are 12 PAH pharmacotherapies approved by the U.S. Food and Drug Administration (FDA) in the United States.⁷ The therapies include a soluble guanylate cyclase stimulator (riociguat); endothelin receptor antagonists (e.g., ambrisentan, bosentan, and macitentan); phosphodiesterase-5 inhibitors (e.g., sildenafil and tadalafil); and prostacyclin analogs (e.g., epoprostenol, treprostinil, iloprost, and selexipag).^{1,7}

Treatment goals for patients with PAH have recently been reported in a consensus statement from the Fifth World Symposium on Pulmonary Hypertension.¹⁵ According to this statement, the goals of treatment are to improve functional class, improve 6-minute walk distance (6MWD) to >440 meters, achieve normalization of right ventricular size and function on an echocardiograph, achieve a decrease or normalization of B-type natriuretic peptide, and improve hemodynamics.¹⁵ Other treatment goals include to prevent disease progression, increase patient survival, and improve health-related quality of life.^{1,12,14} The statement suggests that specific PAH therapy should be augmented to achieve these goals. Similarly, the American College of Cardiology Foundation/American Heart Association treatment guidelines and CHEST Guideline and Expert Panel Report support the use of combination therapy in patients with PAH who have an inadequate response to monotherapy.^{12,16} In clinical practice, many providers already adopt this practice of combination therapy. Based on the REVEAL Registry, 46% of PAH patients were being treated with dual agents, and 9% were being treated with triple therapy.¹⁷ These data are similar to that reported in a study conducted in Germany, in which 43% of patients with PAH were reported as treated with a 2-drug regimen to achieve measurable stabilization of the disease.¹⁸ Unfortunately, while achieving the goals outlined in the Fifth World Symposium statement are likely to be clinically relevant, no randomized clinical trials examining the superiority of such “goal-directed therapy” over conventional clinical management exist.

Treatment of Patients with CTEPH

Unlike PAH, CTEPH, in select cases, can be surgically treated and potentially cured via pulmonary endarterectomy (PEA), which is the preferred treatment in appropriate patients.^{1,2,19} PEA is used only when patients have surgically accessible disease and involves removing intraluminal scar tissue from the affected pulmonary arteries to reduce PVR and improve cardiac output.¹ The procedure is highly successful and, for many patients, results in substantial improvement in

TABLE 1 Description and Interpretation of 6MWD, WHO-FC, and Clinical Worsening

Description	Interpretation
6MWD: A measure of the distance an individual is able to walk over a total of 6 minutes on a hard, flat surface	
Change in 6MWD	<ul style="list-style-type: none"> Assesses change in functional exercise capacity (i.e., indicator of ability to perform daily activities).³⁴ Most PAH medications have been FDA approved based on change in 6MWD as a primary endpoint of clinical trials.⁷ Studies have reported a range (33-50 meters) of clinically meaningful changes in 6MWD. Has modest validity as a surrogate endpoint for clinical outcomes.⁵⁰
6MWD thresholds	<ul style="list-style-type: none"> Absolute value of 6MWD.⁵⁹ There is no specific threshold value that is more clinically significant than any other.⁵⁵ The most widely used threshold as a treatment goal is >440 meters.^{15,59} Certain thresholds may be appropriate for patients of different age groups, and comorbidities should be taken into consideration when determining the 6MWD threshold for the ideal treatment goal.⁵⁹
Change in 6MWD as a component of a composite endpoint	<ul style="list-style-type: none"> A 15% reduction in the 6MWD is clinically meaningful.⁵⁵ Useful as a component of clinical worsening.⁵⁵
WHO-FC: A means of classifying disease severity in PAH according to level of function associated with symptoms	<ul style="list-style-type: none"> Patients are placed into 1 of 4 WHO-FCs dependent on limits of physical activity.⁶¹ As WHO-FC increases from I to IV, limits of physical activity increase.⁶¹ Systematic bias in clinician assignment of WHO-FC is common.⁶⁷
Clinical worsening: Composite endpoint including all-cause mortality, hospitalization due to PAH, and a component of disease progression	<ul style="list-style-type: none"> Clinical worsening can be predictive of proximate risk for subsequent major events (i.e., death, transplantation, or atrial septostomy).⁶⁸ The definition of clinical worsening has varied across studies and is not standardized.⁶⁸

6MWD = 6-minute walking distance; FDA = U.S. Food and Drug Administration; PAH = pulmonary arterial hypertension; WHO-FC = World Health Organization functional class.

symptoms, function, and quality of life.¹⁹ However, between 24% and 37% of patients with CTEPH have inoperable disease.^{9,20-22} Further, up to one third of CTEPH patients have persistent PH after PEA.^{9,22,23} Among these patients with either inoperable or residual CTEPH following PEA, the prescribing of PAH-specific medications (off-label) has increased, with results of a study using an international registry showing 54% of patients with nonoperable CTEPH being treated with a PAH-specific medication.²² Currently, riociguat is the only FDA-approved medication (approved October 2013) for the indication of CTEPH.²⁴

To guide management of patients with PAH and CTEPH it is necessary to have reliable prognostic markers of treatment responsiveness. Endpoints of randomized trials and patient registries are designed to be clinically meaningful; however, they may not directly be associated with healthcare-related economic outcomes of patients.²⁵ In this review, we examined how endpoints from clinical trials and observational studies (i.e., patient registries) reflect patient outcomes for everyday clinical and formulary decision making.

A PubMed literature search was conducted to retrieve published studies, including randomized phase III clinical trials and observational studies, from years 2000 to May 2015 that evaluated the associations between change in 6MWD, 6MWD thresholds, change in WHO-FC, and clinical worsening with outcomes of patients with PAH and CTEPH. Descriptions and interpretation of these assessments are provided in Table 1.

Assessments and Registries

Assessments to evaluate treatment responsiveness among patients with PAH and CTEPH used in clinical trials have included assessment of functional capacity with the 6MWD test, Borg dyspnea score, WHO-FC, clinical worsening, survival, hemodynamics (e.g., lowering PAP, normalized cardiac output), and health-related quality of life measurements.^{1,5} Registries of patients with PAH and CTEPH have also provided substantial information on the characteristics and survival of patients with these diseases (Table 2).^{4,20,26-33} Additionally, these registries have contributed meaningful information for identifying objective assessments that are associated with patient outcomes.²⁷ The majority of the registries track endpoints similar to that of clinical trials and include changes in 6MWD, WHO/ New York Heart Association (NYHA)-FC, and survival.^{4,20,26-33}

Endpoints of Change

For this review, we focused on the endpoints of change in 6MWD, 6MWD thresholds, change in 6MWD as a composite endpoint, change in WHO-FC, and time to clinical worsening, since clinical trial design task forces have recommended using endpoints that reflect disease progression.²⁵

6-Minute Walking Distance Test

For PAH and CTEPH management, the 6MWD test is a commonly performed assessment. It is a measure of functional

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TABLE 2 Registries Specific for Patients with PAH and CTEPH

Registry	Enrollment	Outcomes Measured
Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) (U.S.) ²⁸	3,515	<ul style="list-style-type: none"> • WHO-FC • 6MWD • Cardiopulmonary exercise testing • Pulmonary function testing • Hemodynamic measurements • Hospitalizations • Deaths
Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA/COMPERA-KIDS) (International) ²⁹	~6,000	<ul style="list-style-type: none"> • Survival by subgroup, by treatment strategy, and other factors • Clinical predictors of short-term and long-term clinical outcomes • Relationship between PAH medications and patient outcomes
EXPosure Registry Riociguat in Patients with Pulmonary Hypertension (EXPERT) (international) ³⁰	~900	<ul style="list-style-type: none"> • Number of adverse events/serious adverse events • All-cause mortality
Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre Registry (ASPIRE) (U.K.) ²⁰	1,344	<ul style="list-style-type: none"> • Pulmonary function • WHO-FC • Shuttle walking test • All-cause mortality
National Audit of Pulmonary Hypertension (U.K.) ^{26,31}	482	<ul style="list-style-type: none"> • Pulmonary function tests • 6MWD • Echocardiography: reduction in peak pulmonary artery pressure • Chest x-ray: reduction in cardiothoracic ratio • Quality of life measures (Papworth protocol) • Survival at 6 months and 1 year on prostaglandins and analogues
French National Pulmonary Hypertension (France) ⁴	674	<ul style="list-style-type: none"> • 6MWD • NYHA functional class • Hemodynamics • Survival
Giessen Pulmonary Hypertension Registry (Germany) ³²	1,700	<ul style="list-style-type: none"> • Exercise capacity • NYHA functional class • Hemodynamics
Swedish Pulmonary Hypertension Registry (SPAHR) (Sweden) ³³	252	<ul style="list-style-type: none"> • 6MWD • NYHA functional class • Hemodynamics • Survival

6MWD=6-minute walking distance; CTEPH=thromboembolic pulmonary hypertension; NYHA=New York Heart Association; PAH=pulmonary arterial hypertension; WHO-FC=World Health Organization functional class.

limitation and correlates with peak aerobic capacity.³⁴ The 6MWD test is convenient in that it is a simple, inexpensive, and reproducible test.³⁴ During the 6MWD test, the degree of dyspnea (Borg scale) and oxygen saturation can also be evaluated.³⁵

Change in 6MWD. The change in 6MWD from baseline to trial endpoint has been used as the primary endpoint of several clinical trials involving patients with PAH and CTEPH and is widely accepted by regulatory agencies (Table 3).^{15,23,36-45} The use of the change in 6MWD as a primary endpoint in clinical trials is based on findings from studies which demonstrated that increases in 6MWD are associated with improved clinical outcomes among patients with PAH.⁴⁶⁻⁴⁸ Provencher et al. (2006) conducted a study of 103 patients with PAH and, using Cox regression analysis, found that each increase of 50 meters in 6MWD was associated with increased survival and event-free status.⁴⁶ From a 12-week sildenafil study, Gilbert et al. (2009) estimated a minimally clinically important dif-

ference of 41 meters among patients with PAH that correlated with patient-reported improvement.⁴⁸ Using a distributional- and anchor-based method, which relied on the relationship of change in 6MWD with patient-reported outcomes using the Physical Component Summary Score of the Medical Outcomes Study 36-item short form, Mathai et al. (2012) reported a minimal important difference (MID) of approximately 33 meters among 405 patients with PAH.⁴⁹ In this study, the anchor- and distributional-based estimates of the MID were similar and comparable to estimates of MID for other chronic lung diseases, including chronic obstructive pulmonary disease, emphysema, and idiopathic pulmonary fibrosis.⁴⁹ Despite these studies reporting positive correlations between increased 6MWD and clinical outcome, the results of a pooled analysis of 10 randomized control trials concluded that change in 6MWD has only modest validity as a surrogate endpoint for clinical outcomes.⁵⁰ This pooled analysis revealed a threshold of 41.8 meters, meaning that if treatment with a medication improved

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TABLE 3 Summary of Endpoints of Randomized Phase III Clinical Trials of Patients with PAH and CTEPH, with Clinical Worsening Included as Primary or Secondary Endpoint

Clinical Trial	Primary Endpoints	Secondary Endpoints	Definition of Clinical Worsening
Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy (ARIES) studies ³⁶	Change in 6MWD from baseline to week 12	<ul style="list-style-type: none"> • Time to clinical worsening • Change in WHO-FC • Change in quality of life • Change in Borg dyspnea score • Change in BNP concentration 	The time from randomization to the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, and study withdrawal because of addition of other PAH medications or early escape criteria
Bosentan: Randomized Trial of Endothelin Receptor Antagonist Therapy (BREATH-1) ³⁷	Change in 6MWD from baseline to week 16	<ul style="list-style-type: none"> • Time to clinical worsening • Change in WHO-FC • Change in Borg dyspnea score 	Time to death, lung transplantation, hospitalization for PH, lack of clinical improvement or worsening leading to discontinuation, need for epoprostenol therapy, or atrial septostomy
Bosentan Effects in Inoperable Forms of Chronic Thromboembolic Pulmonary Hypertension study (BENEFiT) ³⁸	<ul style="list-style-type: none"> • Change in PVR from baseline to week 16 • Change in 6MWD from baseline to week 16 	<ul style="list-style-type: none"> • Change in WHO-FC • Change in cardiac index • Change in total pulmonary resistance • Change in mean right arterial pressure • Change in mPAP • Change in mixed venous oxygen saturation at rest • Time to clinical worsening 	Time to death, lung transplantation, or hospitalization due to worsening of PH
Sitaxsentan To Relieve Impaired Exercise (STRIDE-2) ³⁹	Change in 6MWD from baseline to week 18	<ul style="list-style-type: none"> • Change in WHO-FC • Change in Borg dyspnea score • Time to clinical worsening 	Time to death, lung transplantation, hospitalization due to PAH, initiation of new chronic PAH treatment, combined deterioration in WHO-FC and $\geq 15\%$ decrease in 6MWD
Sitaxsentan To Relieve Impaired Exercise-3 (STRIDE-4) ⁴⁰	Change in 6MWD from baseline to week 18	<ul style="list-style-type: none"> • Change in WHO-FC • Time to clinical worsening 	Time to hospitalization for worsening PAH, death, need for heart-lung or lung transplant, atrial septostomy, or addition of any new type of chronic treatment for PAH, or a combination of deterioration in WHO-FC and $> 15\%$ decrease in 6MWD
Aerosolized Iloprost Randomized study (AIR) ⁴¹	<ul style="list-style-type: none"> • Increase of at least 10% in 6MWD • Improvement in the NYHA-FC in the absence of a deterioration in the clinical condition or death 	<ul style="list-style-type: none"> • Change in 6MWD • Change in NYHA-FC • Change in Mahler Dyspnea Index score • Change in hemodynamic variables • Change in quality of life • Clinical worsening 	Death and need for transplantation
Sildenafil Use in Pulmonary Hypertension study (SUPER) ⁴²	Change in 6MWD from baseline to week 12	<ul style="list-style-type: none"> • Change in mPAP • Change in Borg dyspnea score • Change in WHO-FC • Time to clinical worsening 	Time from randomization to death, transplantation, hospitalization for PAH, or initiation of additional therapies for PAH
Pulmonary Arterial Hypertension and Response to Tadalafil study (PHIRST) ⁴³	Change in 6MWD from baseline to week 16	<ul style="list-style-type: none"> • Change in WHO-FC • Time to clinical worsening • Change in Borg dyspnea score • Change in quality of life • Change in hemodynamics 	Time from randomization to death, lung or heart-lung transplantation, atrial septostomy, hospitalization due to worsening PAH, initiation of new PAH-approved therapy, worsening WHO-FC
Pulmonary Arterial Hypertension Soluble Guanylate Cyclase-Stimulator Trial (PATENT-1) ⁴⁴	Change in 6MWD from baseline to week 12	<ul style="list-style-type: none"> • Change in PVR • Change in NT-proBNP • Change in WHO-FC • Time to clinical worsening • Change in Borg dyspnea score • Change in quality of life 	First occurrence of death, heart/lung transplantation, atrial septostomy, hospitalization due to worsening PAH, start of new specific PAH treatment or modification of a pre-existing prostanoid treatment due to worsening PAH, persistent decrease $> 15\%$ 6MWD, persistent worsening of WHO-FC
Chronic Thromboembolic Pulmonary Hypertension sGC-Stimulator Trial (CHEST-1) ⁴⁵	Change in 6MWD from baseline to week 16	<ul style="list-style-type: none"> • Change in PVR • Change in NT-proBNP • Change in WHO-FC • Time to clinical worsening • Change in Borg dyspnea score • Change in quality of life 	First occurrence of death, heart/lung transplantation, rescue PEA, hospitalization due to worsening PH, start of new specific PH treatment, persistent decrease $> 15\%$ 6MWD, persistent worsening of WHO-FC

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TABLE 3 Summary of Endpoints of Randomized Phase III Clinical Trials of Patients with PAH and CTEPH, with Clinical Worsening Included as Primary or Secondary Endpoint (*continued*)

Clinical Trial	Primary Endpoints	Secondary Endpoints	Definition of Clinical Worsening
Selexipag (ACT-293987) in Pulmonary Arterial Hypertension, GRIPHON Trial ⁶⁹	Time to first adjudicated morbidity or mortality event	<ul style="list-style-type: none"> • Change in 6MWD • Change in Borg dyspnea score 	Time to death or hospitalization for worsening of PAH, worsening of PAH resulting in need for lung transplantation, or atrial septostomy, initiation of parenteral prostanoid therapy, chronic oxygen therapy, or disease progression
Macitentan and Morbidity and Mortality in Pulmonary Arterial Hypertension (SERAPHIN) ⁶⁰	Time from initiation of "treatment to first event related to PAH"	<ul style="list-style-type: none"> • Change in 6MWD • Change in WHO-FC • Death due to PAH or hospitalization for PAH • Death from any cause 	Time to worsening of PAH, initiation of treatment with intravenous or subcutaneous prostanoids, lung transplantation, or atrial septostomy, or death. Worsening of PAH was defined by the occurrence of all 3 of the following: a decrease in the 6MWD $\geq 15\%$, worsening of symptoms of PAH, and the need for additional treatment for PAH
A Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects with Pulmonary Arterial Hypertension (AMBITION) ⁷⁰	Number of patients and time to first adjudicated clinical failure event	<ul style="list-style-type: none"> • Change in NT-proBNP • Percentage of patients with a satisfactory clinical response • Change in 6MWD • Change in WHO-FC • Change in Borg dyspnea score 	Clinical failure defined as death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response
Beraprost-314d Added-on to Treprostinil (BEAT) ⁷¹	Time to clinical worsening	<ul style="list-style-type: none"> • Change in 6MWD • Change in Borg dyspnea score • Change in WHO-FC • Change in NT-proBNP 	Time from randomization to the first of any of the following: death, hospitalization due to worsening PAH, initiation of parenteral prostacyclin, directly related to worsening PAH, disease progression, and unsatisfactory long-term clinical response

6MWD=6-minute walking distance; BNP=Plasma B-type natriuretic peptide; CTEPH=chronic thromboembolic pulmonary hypertension; NT-proBNP=N-terminal pro-brain natriuretic peptide; NYHA-FC=New York Heart Association functional class; PAH=pulmonary arterial hypertension; PAP=pulmonary artery pressure; PEA=pulmonary endarterectomy; PH=pulmonary hypertension; PVR=pulmonary vascular resistance.

6MWD over 12 weeks by ≥ 41.8 meters versus treatment with placebo then the medication with 95% confidence is associated with a reduction in clinical event rate over 12 weeks.⁵⁰ However, this change in 6MWD accounted for only 22% of the treatment effect.⁵⁰

Recent evaluation of the relationship of a change in 6MWD and clinical worsening-free survival was conducted on the long-term results of the PATENT-2 and CHEST-2 trials. Two-year results of the PATENT-2 trial showed a significant relationship between a 40-meter improvement from baseline in 6MWD and clinical worsening-free survival among patients with PAH (hazard ratio [HR]=0.80, 95% confidence interval [CI]=0.68-0.94, $P=0.008$).^{51,52} In the PATENT-2 trial, clinical worsening was defined as the first occurrence of any of the following events: death, heart/lung transplantation, atrial septostomy, hospitalization due to worsening of PAH, start of new PAH-specific treatment or modification of existing prostanoid treatment, persistent decrease of $> 15\%$ from baseline in 6MWD, and persistent worsening of WHO-FC.^{51,52} Also, 2-year results of the CHEST-2 trial showed a significant relationship between a 40-meter improvement from baseline in 6MWD and clinical worsening-free survival among patients

with CTEPH (HR=0.77, 95% CI=0.61-0.97, $P=0.03$).^{53,54} In the CHEST-2 trial, clinical worsening was defined similar to that in PATENT-2.^{53,54} These long-term results of the PATENT-2 and CHEST-2 trials provide supporting evidence that a 40-meter change from baseline in 6MWD is useful and clinically meaningful.⁵¹⁻⁵⁴

6MWD Thresholds. Farber et al. (2015) conducted an observational study using the REVEAL Registry, in which the prognostic value of the baseline 6MWD, absolute thresholds of the 6MWD, and change in the 6MWD were evaluated.⁵⁵ The findings of this study showed that regardless of the baseline threshold used (< 165 meters, 165-440 meters, > 440 meters), 1-year survival estimates were lower for patients with a baseline 6MWD below the threshold than for patients with a baseline 6MWD above the threshold (Figure 1).⁵⁵ These findings indicate that there is a survival advantage for patients with PAH associated with having a baseline 6MWD above predefined thresholds, but the study does not provide specific evidence supporting use of these certain thresholds as treatment goals.⁵⁵ In fact, a recent study examining the utility of a goal-directed 6MWD strategy among patients with PAH in a PH Canadian registry failed to show a survival benefit at 1 and 2 years

FIGURE 1 Kaplan-Meier Survival Estimates Based on Absolute 6MWD Thresholds at 165 M and 440 M and All Possible 6MWD Thresholds⁵⁵

Reprinted from Farber HW, Miller DP, McGoon MD, Frost AE, Benton WW, Benza RL. Predicting outcomes in pulmonary arterial hypertension based on the 6-minute walk distance. *J Heart Lung Transplant*. 2015;34(3):362-68. Copyright (2015), Creative Commons Attribution from Elsevier.

Note: One-year survival estimates are shown for patients with a baseline 6MWD < 165 m (blue), 165-440 m (green), and > 440 m (orange). Stars mark the 1-year survival estimates for patients with a 6MWD of > 440-m threshold (white star) and patients with a 6MWD of $\leq$ 165-m threshold (black star).

6MWD=6-minute walking distance; m=meter; SE=standard error.

when compared with conventional management.⁵⁶ Given the previous failures of goal-directed therapies in other disease states (e.g., intensive glucose control to prevent cardiovascular complications in patients with type 2 diabetes,⁵⁷ tight blood pressure control to prevent cardiovascular complications in hemodialysis patients⁵⁸), further studies are needed to validate a goal-directed therapeutic strategy for patients with PAH. The recently published European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines have adopted the previous threshold of > 440 meters as a treatment goal, although it is clarified in the guidelines that lower and higher thresholds may be appropriate for patients of different age groups and that comorbidities should also be taken into consideration when determining the 6MWD threshold for the ideal treatment goal.⁵⁹

Change in 6MWD as a Component of a Composite Endpoint.

Farber et al. reported that a 15% reduction in the 6MWD was associated with significantly lower survival at 1 year, but improvement in 6MWD was not associated with better survival.⁵⁵ Thus, Farber et al. concluded that a 15% reduction in

6MWD may be clinically meaningful, and the use of a 15% reduction in the 6MWD as a criterion for PAH worsening in clinical studies is supported.⁵⁵ A $\geq 15\%$ decrease in 6MWD has been used as a component of the composite endpoint of time to clinical worsening in several clinical trials (Table 2).^{39,40,44,45,60}

World Health Organization Functional Class

The functional classes (FCs) for categorizing patients with PAH were initially developed for patients with heart failure by the NYHA and then adapted to patients with PH by the WHO.⁶¹ PH patients are placed into 1 of 4 WHO-FCs dependent on limits of physical activity (e.g., WHO-FC III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope).^{12,61} Several studies have demonstrated that FC is strongly predictive of survival/mortality among patients with PAH.^{1,12,62-64} An analysis of the REVEAL Registry demonstrated that patients with PAH who improved from FC III to FC I/II within 1 year had a significantly better 3-year survival than patients who remained in FC III or worsened to FC IV (84% vs.

FIGURE 2 Survival Among Patients with PAH According to Functional Class⁶⁴

Number at Risk													
	0	3	6	9	12	15	18	21	24	27	30	33	36
Improved FC III→FC I/II	263	260	258	254	244	236	233	225	221	214	200	194	187
Unchanged FC III	645	612	576	554	536	517	498	469	447	418	393	371	347
Worsened FC III→FC IV	74	56	43	38	34	30	27	25	21	20	17	16	15

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FC=functional class; PAH=pulmonary arterial hypertension.

66%; Figure 2).⁶⁴ The results of this REVEAL Registry analysis additionally showed that improvement in FC affects survival independently of PAH cause or time of diagnosis.⁶⁴ Barst et al. (2013) concluded from this study that FC status is a meaningful clinical parameter.⁶⁴ Furthermore, changes in 6MWD correlated with WHO-FC, such that 6MWD increased during the study period for those who improved in WHO-FC but decreased for those who worsened in WHO-FC.⁶⁴ The results of Barst et al. were similar to that of Nickel et al. (2012), who conducted a prospective, single-center study of 109 patients with idiopathic PAH.^{64,65} In this study, a deterioration in WHO-FC between baseline and follow-up was associated with twice the risk of death (HR=2.0, $P=0.02$).⁶⁵ Two-year results of the PATENT-2 and CHEST-2 trials did not show significant correlations between a deterioration in WHO-FC from baseline and survival among patients with PAH or CTEPH.^{52,54} However, they did show significant correlations between a deterioration in WHO-FC and clinical worsening-free survival (PATENT-2: HR=0.55, 95% CI=0.35-0.87, $P=0.01$; CHEST-2: HR=0.47, 95% CI=0.27-0.84, $P=0.01$).^{52,54} The results of these studies provide strong evidence that WHO-FC is a prognostic indicator of survival/clinical worsening-free survival among patients with PAH or CTEPH.^{52,54,62-65} The results of a German study conducted on patients with severe PH showed that exer-

cise training plus medical therapy versus medical therapy alone reduces deterioration of WHO-FC, which is associated with less health care resource utilization.⁶⁶

There are no other studies in the published literature showing any evidence supporting that changes in WHO-FC correspond with changes in health care resource utilization and costs. Limitations in the utility of WHO-FC as an outcome measurement for assessing response to therapy exist. For example, there is significant variability in the inter-rater reliability of assignment of FC as demonstrated by Taichman et al. (2009).⁶⁷ In this study, clinicians highly familiar with PAH patients were asked to assign WHO-FC to several patient case scenarios.⁶⁷ Responses varied widely; in fact, there was no agreement on WHO-FC for any of the case presentations, and systematic bias in assignment of WHO-FC between clinicians was found.⁶⁷ These factors limit the utility of change in WHO-FC alone as a reliable tool in the assessment of response to therapy among patients with PAH or CTEPH.

Clinical Worsening

The Task Force on End Points and Clinical Trial Design at the Fourth World Symposium on Pulmonary Hypertension recommended that time to clinical worsening (TTCW), also referred to as clinical worsening and disease progression,

be used as a primary endpoint in phase III trials.^{1,13,25} This point was reiterated at the Fifth World Symposium in 2013 and also recommended by the 2008 Dana Point Task Force on End Points and Clinical Trial Design.⁶⁷ The proposed definition of clinical worsening includes all-cause mortality, nonelective hospitalization for PAH, and disease progression.¹ The Fourth World Symposium task force recommended that disease progression be defined as “a reduction from baseline in the 6MWD by 15%...plus worsening functional class (except for patients already in functional class IV).”^{1,68} Using the REVEAL Registry, Frost et al. (2013) validated clinical worsening as predictive of proximate (within 1 year) risk for subsequent major events (i.e., death, transplantation, or atrial septostomy).⁶⁸ In this study of 3,001 patients with PAH, freedom from clinical worsening was defined as freedom from (a) worsening FC, (b) a $\geq 15\%$ reduction in 6MWD, (c) all-cause hospitalization, or (d) the introduction of parenteral prostacyclin analog therapy.⁶⁸ The study showed that among patients who survived without transplantation or septostomy (77.7% vs. 94.1%, $P < 0.001$), were newly diagnosed patients (74.6% vs. 90.3%, $P < 0.001$), and previously diagnosed patients (77.6% vs. 95.1%, $P < 0.001$), those who clinically worsened in the first year had poorer survival in the subsequent year than those who did not.⁶⁸ Among the overall study population, PAH patients with a clinical worsening event had a mean of 7.2 months until death.⁶⁸ In this observational study, clinical worsening was highly predictive of subsequent proximate mortality, validating clinical worsening as a meaningful prognostic tool in clinical practice and as a primary endpoint in clinical trial design.⁶⁸ The definition of clinical worsening used by Frost et al. was slightly different from that of the Fourth World Symposium task force in that all-cause hospitalization was used rather than nonelective hospitalization, and worsening FC and 6MWD were not required to be concurrent; thus, worsening FC *or* worsening 6MWD, rather than worsening FC *and* worsening 6MWD, was used in their definition.⁶⁸

Clinical worsening has been included as a primary or secondary endpoint in several clinical trials (Table 2).^{36-45,60,69-71} However, the definition of clinical worsening varied across trials and was not standardized, so comparison of treatment efficacy using TTCW as the outcome measure is challenging.⁶⁸ Significant differences in clinical worsening have not been observed in all trials with PAH-specific medications but have been in some, including ARIES-2 (ambrisentan vs. placebo),³⁶ BREATH-1 (bosentan vs. placebo),³⁷ and PATENT-1 (riociguat vs. placebo).⁴⁴ The main drivers of significant differences in clinical worsening varied across trials but were most

frequently a decrease in hospitalizations for PH, deterioration in WHO-FC, a decrease in 6MWD, and initiation of a new PAH treatment.^{36,37,44} Significant differences in clinical worsening is an important attribute of a PAH-specific medication as it substantiates an indication for treatment of PAH to increase exercise ability and to decrease/delay clinical worsening. Having clinical worsening as a primary endpoint in clinical trials and using a universal definition will be useful for comparing treatments, especially among combination therapies, and also will assist in the identification of PAH and CTEPH patients who require therapy augmentation.^{17,68}

Discussion

Management, including earlier diagnoses and advancement in pharmacologic treatments of patients with PAH and CTEPH, has improved in the recent past, and patients with these diseases are living longer.⁷ In view of the greater number of medications available to treat PAH, the introduction of the first approved therapy to treat CTEPH, and the increasing use of combination pharmacotherapy, reliable prognostic markers of treatment responsiveness are important to help guide appropriate management.^{7,9,17} Based on this review of published literature, a reduction in 6MWD as a criterion for PAH worsening, a deterioration in WHO-FC, and delay in the time to clinical worsening are clinically meaningful trial endpoints and are associated with outcomes of patients with PAH and CTEPH. As previously mentioned, there are currently limitations for these endpoints, including that studies do not agree on the exact 6MWD change that correlates with patient outcomes; the definition of WHO-FCs varies among physicians and there is bias in assignment of WHO-FC; and that a universal definition of clinical worsening has not yet been used systematically in studies.

Utilization and standardization of these endpoints will be useful for comparing interventions of clinical trials and for goal-oriented therapy. Clinical trials involving patients with PAH and CTEPH are evolving to include a universal, composite endpoint of clinical worsening as a primary endpoint, which will help better define the effect of treatments on clinical outcomes that are notable for evaluating quality of care and cost-effectiveness of treatments.¹⁴ This evolution is critical, since many studies have found that the health care and economic burdens of patients with PAH and CTEPH are substantial,⁷²⁻⁸¹ although, because of the lack of specific coding for these rare diseases, there is a level of uncertainty regarding the true burden of PAH and CTEPH. Given the high health care costs of PAH and CTEPH patients, better management of both diseases with targeted pharmacotherapies may result in cost offsets

from reduced hospitalizations, lengthy hospital stays, and physician visits. From a U.S. payer perspective, clinical worsening is an important composite endpoint in that it includes hospitalization, which can be transformed into a preventative cost value associated with efficacious treatment of patients with PAH and CTEPH.

Except for the recently completed AMBITION trial,⁷⁰ in which abiristatant monotherapy, tadalafil monotherapy, and abiristatant and tadalafil combination therapy were compared, there have been no published comparative studies across PAH-specific treatments; therefore, it is difficult to assess which treatments are “the most efficacious.” The new ESC/ERS 2015 guidelines for diagnosis and treatment of PH give drug recommendations for monotherapy and combination therapy for the treatment of patients with PAH according to WHO-FC.⁵⁹ However, because there are no head-to-head comparative studies of the different drugs, the guidelines do not propose a specific first-line therapy.⁵⁹ The guidelines also do not specify if combination therapy should be used initially for patients with PAH WHO-FC II-III, but they do note that sequential combination therapy (i.e., first monotherapy then addition of a second and third drug in patients with inadequate clinical results) is the most widely used strategy in clinical trials and routine clinical practice.⁵⁹ Thus, clinicians must use their best judgment to determine which patients may benefit from specific treatments. For patients with CTEPH, there is only 1 approved medication.²⁴

Conclusions

As new clinical trials and studies of patient registries are conducted, it will be important for them to maintain universal endpoints so that health care providers, decision makers, and payers can better understand the value of targeted pharmacotherapies and combination therapies for the treatment of patients with PAH and CTEPH.

Authors

CHRISTINE DIVERS, PhD; DAVID PLATT, MD; and EDWARD WANG, PharmD, MBA, Bayer HealthCare Pharmaceuticals, Whippany, New Jersey. JAY LIN, PhD, MBA, and MELISSA LINGOHR-SMITH, PhD, Novosys Health, Green Brook, New Jersey. STEPHEN C. MATHAI, MD, MHS, Johns Hopkins University School of Medicine, Baltimore, Maryland.

AUTHOR CORRESPONDENCE: Christine Divers, PhD, Director, HEOR Field Team, U.S. Health Economics and Outcomes Research, Bayer HealthCare Pharmaceuticals, 100 Bayer Blvd., Whippany, NJ 07981. Tel.: 919.924.8484; E-mail: christine.divers@bayer.com.

DISCLOSURES

Sponsorship for this review and article processing charges were funded by Bayer HealthCare Pharmaceuticals. Divers and Platt are employees of Bayer HealthCare Pharmaceuticals. Wang is an employee of Bayer HealthCare Pharmaceuticals and owns stock in the company. Lin and Lingohr-Smith are employees of Novosys Health, which received research funds from Bayer HealthCare Pharmaceuticals in connection with conducting this review and developing this manuscript. Mathai is a consultant to Bayer HealthCare Pharmaceuticals and also reports consulting fees from Actelion and Gilead.

Study concept and design were contributed by Divers, Platt, Lin, and Mathai. Lin and Lingohr-Smith collected the data, and data interpretation was performed by Divers, Platt, Wang, and Mathai. The manuscript was written primarily by Lingohr-Smith, with assistance from the other authors, and revised by Divers, Platt, Wang, and Mathai.

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