The Role of Noninvasive Endpoints in Predicting Long-Term Outcomes in Pulmonary Arterial Hypertension

Samantha L. Wronski1 · Margaret Mordin2 · Kim Kelley3 · Rebekah H. Anguiano4 · Peter Classi5 · Eric Shen5 · Scott Manaker6

Received: 25 July 2019 / Accepted: 29 October 2019 / Published online: 13 November 2019
© The Author(s) 2019

Abstract

Background Until recently, many clinical trials in patients with pulmonary arterial hypertension (PAH) evaluated exercise capacity with 6-minute walk distance (6MWD) as the primary endpoint. Common secondary endpoints include PAH functional class (FC), which assesses symptoms, and either brain natriuretic peptide (BNP) or the inactive N-terminal cleavage product of its prohormone (NT-proBNP), which assesses cardiac function.

Objective Examine the relationships among 6MWD, FC, and BNP/NT-proBNP measured at baseline or follow-up with long-term outcomes in PAH studies.

Methods Relevant literature from January 1990 to April 2018 were obtained by searching PubMed, Embase, and Cochrane. Articles in English reporting on associations between 6MWD, FC, or BNP/NT-proBNP and outcomes in PAH were identified. Each endpoint was evaluated individually. Prespecified inclusion and exclusion criteria were applied at level 1 (titles/abstracts) and level 2 (full-text review).

Results The database search yielded 836 unique records; 65 full-text articles were reviewed. Twenty-five studies were eligible for inclusion. Findings supported the importance of measuring PAH noninvasive endpoints in predicting long-term outcomes. Patients with shorter or decreased 6MWD, poor (III/IV) or declining FC (e.g., from II to III), or elevated or increasing BNP/NT-proBNP had a higher risk of death and costly events (e.g., hospitalization, lung transplant). FC also predicted health care resource utilization and costs. Collectively, these endpoints establish risk groups that predict likelihood of complications from PAH or death.

Conclusion Assessment of 6MWD, FC, and BNP/NT-proBNP provides low-cost, efficient, and noninvasive means of predicting long-term health and economic outcomes in patients with PAH.

Keywords PAH · Noninvasive endpoint · Risk assessment

Introduction

With an estimated prevalence of 10.6–12.4 cases per million [1], pulmonary arterial hypertension (PAH) is a rare chronic and progressive disease characterized by increased pulmonary vascular resistance that can result in death due to right heart failure [2]. Numerous available treatments for PAH [3] have been evaluated in clinical trials using a variety of endpoints [4–6]. In the past two decades, PAH study design and duration shifted from short-term trials assessing noninvasive endpoints to long-term event-driven trials [7, 8].

Six-minute walk distance (6MWD), functional class (FC), and indicators of right ventricular function (i.e., brain natriuretic peptide [BNP]/the active N-terminal cleavage product of its prohormone [NT-proBNP], described in Table 1) are

---

1 RTI Health Solutions, Research Triangle Park, NC, USA
2 RTI Health Solutions, Ann Arbor, MI, USA
3 Rx Trusted Advisors, Phoenix, AZ, USA
4 Department of Pharmacy Practice, University of Illinois at Chicago, Chicago, IL, USA
5 United Therapeutics, Research Triangle Park, NC, USA
6 Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
among the commonly used short-term primary and secondary noninvasive endpoints in clinical PAH trials [9, 10]. In a literature review examining 126 pulmonary hypertension (PH) clinical trials (78% in PAH) from 1985 to 2013, surrogate measures were primary endpoints in 95% of trials and secondary endpoints in 33% of trials [9]. 6MWD and FC were among the noninvasive endpoints that were used significantly more frequently ($P < 0.0001$) [9]. The latest 2015 European Society of Cardiology/European Respiratory Society treatment guidelines [11] and registry studies such as COMPERA [12] and REVEAL [13] also include 6MWD, FC, and BNP/NT-proBNP as important components of risk assessment. Collectively, 6MWD, FC, and BNP/NT-proBNP serve as measurable prognostic indicators of the distal outcomes of morbidity and mortality that may be assessed early in order to determine treatment course and improve outcomes [14, 15]. However, the clinical relevance and ability of these noninvasive endpoints to consistently correlate with key indicators of disease progression, such as hospitalization and death, has received mixed support [16–25]. This, coupled with improvements in survival and quality of life that have allowed recent clinical trials to follow patients with PAH for 4–6 years [7], has led to the prominence of mortality and morbidity as endpoints.

Morbidity and mortality, a term reflecting clinical worsening and disease progression [16, 23, 26], provide a robust demonstration of efficacy, safety, and long-term benefits of treatments for PAH [23]. The use of clinical worsening or disease progression as a primary endpoint in phase 3 trials was endorsed by the Task Force on End Points and Clinical Trial Design of both the Fourth and Fifth World Symposium on Pulmonary Hypertension and the 2008 Dana Point Task Force on End Points and Clinical Trial Design [16]. However, comparison of treatment efficacy across trials may be hindered by the varying definitions used for clinical worsening, as seen when comparing the definitions used in the AMBITION [27], GRIPHON [28], SERAPHIN [29], and FREEDOM EV [30–32] clinical trials. While it has been argued that the composite endpoint of clinical worsening is more clinically meaningful than noninvasive endpoints [19, 25], all four trials include 6MWD and FC in their definitions of clinical worsening, despite other differences. Additional components in the definition of clinical worsening, such as death, hospitalization, and lung transplant, require long-term follow-up to assess, and despite clearly indicating clear and undisputable indicators of ultimate treatment efficacy and safety, they cannot be used to assess clinical risk in the day-to-day care of patients with PAH that guide treatment decisions.

There is a need to revisit the optimal duration of future trials [7] and include clinically meaningful endpoints that reflect how patients feel and function [33]. In addition, the use of universal endpoints in PAH clinical trials and observational studies would better inform health care providers, decision makers, and payers on the value of targeted pharmacotherapies and combination therapies for patients with PAH [16]. 6MWD, FC, and BNP/NT-proBNP are universal endpoints, routinely used in clinical risk assessment, that can be assessed short-term (12–16 weeks [23]). The present review examines the value of 6MWD, FC, and BNP/NT-proBNP by summarizing the literature supporting the relationship between these noninvasive endpoints and long-term clinical and economic outcomes.
Methods

A literature review was conducted on April 13, 2018, in PubMed, Embase, and the Cochrane Database of Systematic Reviews using a search strategy (Table 2) that included Medical Subject Headings (MeSH) and key words for disease (e.g., pulmonary arterial hypertension), endpoints (e.g., 6MWD, FC, BNP), clinical importance (e.g., survival, mortality), and economic importance (e.g., costs, readmission, economics). Inclusion criteria incorporated studies published after January 1, 1997, in English and human subjects; comments, letters, or editorials were excluded. Bibliographies of relevant review articles were reviewed for any pertinent articles unidentified in the original search. To obtain information from relevant unpublished studies, a search of 2016–2017 conference abstracts via Embase was performed, including the American Thoracic Society International Conference, American College of Chest Physicians (CHEST) Annual Meeting, CHEST World Congress Annual Meeting, and the International Society for Pharmacoeconomics and Outcomes Research International Meeting.

Table 2 PubMed search strategy (search conducted April 13, 2018)

| Search number | Search terms | Number of results |
|---------------|--------------|-------------------|
| Disease       | “Familial Primary Pulmonary Hypertension”[Majr] OR “pulmonary arterial hypertension”[Title/Abstract] OR “primary pulmonary hypertension”[Title/Abstract] OR “idiopathic pulmonary hypertension”[Title/Abstract] | 9301 |
| Endpoints     | 1 AND (“six minute walk”[Title/Abstract] OR “6 min walk”[Title/Abstract] OR “6MWD”[Title/Abstract] OR “6MWT”[Title/Abstract] OR “New York Heart Association Functional Class”[Title/Abstract] OR “NYHA functional class”[Title/Abstract] OR “NYHA FC”[Title/Abstract] OR “World Health Organization Functional Class”[Title/Abstract] OR “WHO functional class”[Title/Abstract] OR “WHO FC”[Title/Abstract] OR “brain natriuretic peptide”[Title/Abstract] OR “pro-brain natriuretic peptide”[Title/Abstract] OR “BNP”[Title/Abstract] OR “NT-proBNP”[Title/Abstract] OR “Natriuretic Peptide, Brain”[Majr]) | 1208 |
| Clinical importance | 2 AND (“Disease Progression”[Majr] OR “Familial Primary Pulmonary Hypertension” mortality”[Majr] OR “Mortality”[Majr] OR “Familial Primary Pulmonary Hypertension/comlications”[Majr] OR “Survival”[Majr] OR “Comorbidity”[Majr] OR “Quality of Life”[Majr] OR “quality of life”[Title] OR “risk”[Title] OR “survival”[Title] OR “mortality”[Title] OR “death”[Title] OR “prognosis”[Title] OR “disease progression”[Title/Abstract] OR “disease exacerbation”[Title/Abstract] OR “complication”[Title/Abstract] OR “sequela”[Title/Abstract] OR “comorbidity”[Title/Abstract] OR “multimorbidity”[Title/Abstract] OR “fatal”[Title/Abstract] OR “life quality”[Title/Abstract] OR “QoL”[Title/Abstract] OR “hrqol”[Title/Abstract] OR “hrql”[Title/Abstract]) | 370 |
| Economic importance | 4 AND (“Patient Readmission”[Majr] OR “Hospitalization”[Majr] OR “Length of Stay”[Majr] OR “Fees and Charges”[Majr] OR “Health Care Costs”[Majr] OR “Costs and Cost Analysis”[Majr] OR “Economics”[Majr] OR “Economics, Hospital”[Majr] OR “Economics, Medical”[Majr] OR “Economics, Nursing”[Majr] OR “Economics, Pharmaceutical”[Majr] OR “Budgets”[Majr] OR “Health Expenditures”[Majr] OR “Cost of Illness”[Majr] OR “Cost–Benefit Analysis”[Majr] OR “hospital”[Title/Abstract] OR “length of stay”[Title/Abstract] OR “stay length”[Title/Abstract] OR “readmission”[Title/Abstract] OR “readmit”[Title/Abstract] OR “cost”[Title/Abstract] OR “costs”[Title/Abstract] OR “costly”[Title/Abstract] OR “economic”[Title/Abstract] OR “fiscal”[Title/Abstract] OR “fee”[Title/Abstract] OR “fees”[Title/Abstract] OR “expenditure”[Title/Abstract] OR “budget”[Title/Abstract]) | 172 |
| Exclusions    | “Animals”[MeSH] NOT “Humans”[MeSH] | 2,060,466 |
|               | “Comment”[Publication Type] OR “Letter”[Publication Type] OR “Editorial”[Publication Type] | 1,104,425 |
|               | (“Child”[MeSH] OR “Infant”[MeSH] OR “Adolescent”[MeSH] OR “child”[Title/Abstract] OR “infant”[Title/Abstract] OR “newborn”[Title/Abstract] OR “adolescent”[Title/Abstract]) NOT (“Adult”[MeSH] OR “adult”[Title/Abstract] OR “elder”[Title/Abstract] OR “senior citizen”[Title/Abstract] OR “middle age”[Title/Abstract]) | 937,574 |

Search terms and limits were adapted for searching in Embase and the Cochrane Database of Systematic Reviews. Limits include 1997–present; English; humans; adults; no comments, letters, editorials.
 Titles and abstracts of records were reviewed (level 1 screening) according to the objectives and inclusion and exclusion criteria. Included studies, defined using PICOS (population, intervention, comparison, outcome, study type), had the following:

- A primarily adult population (≥ 18 years) with PAH from a WHO group 1 etiology
- Any intervention or comparator
- At least one of the noninvasive endpoints—6MWD, FC, BNP/NT-proBNP (Table 1)—and reported on the relationship between a noninvasive endpoint and a clinical or economic outcome of interest (note that the literature was searched for individual associations between each of the endpoints and PAH outcomes)
- An interventional (e.g., randomized controlled trials) or noninterventional (e.g., observational, prospective, retrospective, database, and/or registry studies) design, with ≥ 75 patients, or a relevant literature review.

Full texts of included studies were reviewed (level 2 screening) using the same relevance criteria applied at level 1. That is, full-text articles were reviewed in detail, and the inclusion and exclusion criteria applied at level 1 (title/abstract screening) were applied to evaluate the appropriateness for inclusion.

Results

Literature Review

Figure 1 summarizes the literature review, which identified 836 unique studies for level 1 screening, including 64 conference abstracts and 1 study identified through desktop research. Of these, 65 records were selected for level 2 screening; no conference abstracts were deemed eligible for inclusion. Twenty-five studies, summarized in Table 3, were selected for inclusion according to predefined inclusion/exclusion criteria. Although outcomes, such as risk of death or the combined endpoint of risk of death or lung transplant, were consistently defined across the literature, clinical worsening was defined differently in each of the three studies evaluating it as an outcome [2, 34, 35]; definitions used are noted in Table 3.

---

**Fig. 1** Literature review flow diagram
| References                  | Study type                     | Description                                                                 | Timeframe                      | Sample size | Population                                                                 |
|-----------------------------|--------------------------------|------------------------------------------------------------------------------|-------------------------------|-------------|-----------------------------------------------------------------------------|
| Frantz et al. [52]          | Prospective registry (REVEAL)  | REVEAL Registry                                                              | 2006–2012                     | 1426        | WHO group 1 PAH (confirmed by right-sided heart catheterization)           |
| Kylhammar et al. [55]       | Observational registry (SPAHR) | Study of incident cases of patients classified into PAH risk groups, determined on the basis of multiple noninvasive measurements, including WHO FC, 6MWD, NT-proBNP, and echocardiography imaging and hemodynamics | January 1, 2008–March 1, 2016  | 530         | PAH diagnoses included idiopathic/familial PAH, CTD-associated PAH, CHD-associated PAH, or other forms of associated PAH (drug- and toxin-induced, HIV-associated, and portal-hypertension-associated PAH) |
| Snipelisky et al. [47]      | Retrospective                  | Review of patients at University of Pittsburgh Medical Center. NYHA FC was extracted from electronic medical record. From a sample of 273 patients, 163 had documented serum albumin concentration and comprised the final study population | March 2001–August 2008         | 163         | WHO group 1 PAH                                                             |
| Souza et al. [37]           | RCT                            | SERAPHIN multicenter, randomized controlled, event-driven study assessing the long-term efficacy and safety of macitentan | May 2008–April 2012           | 742         | PAH (WHO FC II-IV) diagnosed by right heart catheterization with idiopathic PAH, heritable PAH, or PAH related to connective tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV infection, drug use, or toxin exposure |
| Weatherald et al. [45]      | Retrospective registry (French Pulmonary Arterial Hypertension Network Registry) | Review of patients enrolled in a registry                                       | 2006–2016                     | 981         | Diagnosed with idiopathic, heritable, or drug-induced PAH who had at least 1 follow-up RHC |
| Zelniker et al. [38]        | Prospective registry (COMPERA) | Multinational, prospective registry that enrolls patients with newly diagnosed PAH who receive targeted medical therapy; all patients underwent right heart catherization | June 2007–January 2016        | 2391; Survival analysis = 2178 | Newly diagnosed PAH; etiologies included idiopathic/drug-associated or hereditary PAH, connective tissue disease, HIV-associated PAH, portopulmonary hypertension, and congenital heart disease |
| Boucly et al. [54]          | Retrospective registry         | Review of all incident (newly diagnosed) patients enrolled in a French registry | 2006–2016                     | 603         | Idiopathic, heritable, or drug-and toxin-induced PAH                       |
| References       | Study type                             | Description                                                                 | Timeframe                      | Sample size | Population                                                                 |
|------------------|----------------------------------------|------------------------------------------------------------------------------|--------------------------------|-------------|-----------------------------------------------------------------------------|
| Dufour et al. [6] | Retrospective                          | Observational cohort study based on de-identified administrative claims data from the Humana Research Database. Data sources included medical and pharmacy claims, and enrollment records. ~70% of the database included patients with Medicare Advantage plans, and ~30% included patients with commercial insurance | January 1, 2009–June 30, 2014 | 476         | Patients had at least one claim for a PAH-specific medication during the study period, and at least one medical claim with one relevant diagnosis code associated with PH in any position on the administrative medical claim form or at least one medical claim with a CPT or ICD-9-CM code indication at right heart catheterization during the identification period; ICD-9 diagnosis codes included 416.0 (primary pulmonary hypertension), 416.8 (other chronic pulmonary heart diseases), or 416.9 (chronic pulmonary heart disease, unspecified) |
| Hoeper et al. [12] | Prospective registry (COMPERA) | Patients with newly diagnosed PAH were classified according to risk using the strategy proposed by the European PH guidelines, which consider WHO FC, 6MWT, BNP/NT-proBNP, right atrial pressure, cardiac index, and mixed venous oxygen saturation | January 1, 2009–December 1, 2016 | 1588        | Treatment-naive, newly diagnosed PAH; etiologies included idiopathic/drug-associated or hereditary PAH, connective tissue disease, HIV-associated PAH, portopulmonary hypertension, and congenital heart disease |
| Tang et al. [35] | Prospective                            | Analysis of patients who were admitted to Fuwai Hospital and underwent symptom-limited cardiopulmonary exercise testing. Clinical worsening was defined as the time from cardiopulmonary exercise testing to the first event, which included the following: all-cause mortality, lung transplant, hospitalization for worsening of PAH, the need for epoprostenol therapy, and interventional procedures (performance of balloon atrial septostomy) | November 11, 2010–June 25, 2015 | 210         | Newly diagnosed idiopathic PAH                                             |
Table 3 (continued)

| References          | Study type | Description                                                                 | Timeframe          | Sample size | Population                                                                 |
|---------------------|------------|-----------------------------------------------------------------------------|--------------------|-------------|-----------------------------------------------------------------------------|
| Ghofrani et al. [2] | RCT        | Patients from the PATENT-1 study who entered the PATENT-2 open-label extension | March 12, 2009–March 1, 2014 | 396         | PAH etiologies included idiopathic PAH, familial PAH, connective tissue disease, systemic-sclerosis–associated PAH, congenital heart disease, portal pulmonary, anorexic or amphetamine-associated PAH |
| Huang et al. [34]  | Retrospective | Analysis of patients from the Southwest Ontario Pulmonary Hypertension Clinical of the Western University | Not specified      | 100         | WHO group I PAH; diagnoses included idiopathic PAH, CTD PAH, and CHD PAH   |
| Ozpelit et al. [36] | Prospective | Consecutive adult patients with definitive PAH who attended the PAH Clinic, Department of Cardiology, School of Medicine, Dokuz Eylul University, Izmir, Turkey | January 2008–June 2014 | 101         | Definitive PAH; patients with overt infections disease at the time of PAH diagnosis were excluded |
| Zelniker et al. [43]| Prospective | Patients enrolled in the outpatient department of the University Hospital of Heidelberg, Germany (referral center for PAH patients) | January 2010–May 2010 | 95          | Confirmed PAH (Dana point group 1); diagnoses were categorized as idiopathic PAH, PAH and connective tissue disease, other |
| References       | Study type                          | Description                                                                 | Timeframe               | Sample size | Population                                                                 |
|------------------|-------------------------------------|-----------------------------------------------------------------------------|-------------------------|-------------|----------------------------------------------------------------------------|
| Ehlken et al. [53] | Prospective                        | German prospective analysis, patients with severe PAH receiving exercise training plus medical therapy compared with patients who received medical therapy alone | Semistructured phone interviews were performed in April 2007 to assess survival and clinical status of the patients | Training group = 58 Retrospective control group = 46 | PAH etiologies included idiopathic and familial; PAH associated with collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, or HIV; PH associated with the following lung diseases: chronic obstructive pulmonary disease, interstitial lung disease, chronic thromboembolic pulmonary hypertension, or other causes |
| Barst et al. [49]  | Prospective Registry (REVEAL)       | Using the REVEAL registry, patients with were classified as improved, unchanged, or worsened according to their change in FC from enrollment to first follow-up within 1 year (mean ± SD: 4 ± 3 months) | Not specified (REVEAL data spanned 2006-2012) | 982 | WHO group I NYHA/WHO FC III PAH |
| Fritz et al. [40]   | Retrospective (analysis of 2 RCTs)  | Pooled analysis of patients enrolled in 2 RCTs (Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multi-center, Efficacy Study 1/2 [ARIES-1 and ARIES-2]) who had 2-year follow-up | January 2004–February 2006 | 370 | PAH etiologies were idiopathic, connective tissue disease, and other (unspecified) |
| Tiede et al. [50]  | Prospective registry (Giessen Pulmonary Hypertension Registry Study) | Registry containing a total of ~2500 patients at a single specialized referral center (the Giessen Pulmonary Hypertension Center, Universities of Giessen and Marburg Lung Center, University Hospital Giessen, Giessen, Germany) | 1991–2013 | ~700 | Newly diagnosed WHO group 1 PAH (according to Dana Point classification) |
| Batal et al. [41] | Retrospective                       | Review of records of consecutive patients with PAH who underwent diagnostic RHC at the Cleveland Clinic, consisting of those who died within 2 years (reduced survival) and those who survived ≥5 years (long survival group) | February, 1996–January, 2006 | Reduced survival = 21; long survival = 60 | PAH etiologies were idiopathic and scleroderma |
| References          | Study type                     | Description                                                                 | Timeframe                          | Sample size | Population                                                                 |
|---------------------|--------------------------------|-----------------------------------------------------------------------------|------------------------------------|-------------|-----------------------------------------------------------------------------|
| Nickel et al. [46]  | Prospective                    | German cohort database study from Hanover Medical School of patients who had undergone at least 1 follow-up RHC within the first year after PAH-targeted therapy had been initiated | 1999–2009                          | 109         | Newly diagnosed with idiopathic PAH                                       |
| Benza et al. [44]   | Retrospective (analysis of three RCTs) | Review of patients who were enrolled in three trials (P01: 04, 05, 06) treated with subcutaneous treprostinil | June 25, 1998–December 1, 2003     | 811         | PAH etiology: idiopathic, associated PAH, connective tissue disease, congenital heart disease, portopulmonary hypertension |
| Kane et al. [48]    | Retrospective                  | Retrospective single-center study of consecutive patients at the Mayo Clinic Rochester | January 1, 1995–December 31, 2004  | 484         | Fulfilled the contemporary diagnostic criteria for WHO group 1 PAH. Diagnoses included idiopathic, familial, or anorexigenic PAH, PAH in the setting of connective tissue disease, and PAH associated with congenital systemic-to-pulmonary shunts, portal hypertension, and HIV |
| Mauritz et al. [51] | Retrospective                  | Analysis of patients from the Department of Pulmonology of VU Medical Center of Amsterdam (The Netherlands) | November 2002–September 2009       | 198         | WHO group 1 PAH diagnoses included idiopathic PAH, associated connective tissue disease, associated portal hypertension, associated HIV infection, drug- and toxin-induced PAH, other |
| Benza et al. [39]   | Prospective registry (REVEAL)  | Patients consecutively enrolled in the US REVEAL registry                   | Not specified (registry began in 2006) | 2716        | WHO group 1 PAH including idiopathic and familial PAH                      |
| Humbert et al. [42] | Prospective registry (French Network on Pulmonary Hypertension Prospective Registry) | Consecutive patients seen in 17 university pulmonary vascular centers and followed for 3 years | October 2002–October 2003 and followed for 3 years | 354 (56 were incident and 298 were prevalent cases) | Idiopathic, familial, or anorexigen-associated PAH |

6MWD 6-minute walk distance, 6MWT 6-Minute Walk Test, BNP brain natriuretic peptide, CHD congenital heart disease, CPT Current Procedural Terminology, CTD connective tissue disease, FC functional class, ICD-9-CM International Classification of Diseases, Ninth Revision, Clinical Modification, NT-proBNP BNP/the inactive N-terminal cleavage product of its prohormone, NYHA New York Heart Association, PAH pulmonary arterial hypertension, PH pulmonary hypertension, RCT randomized controlled trial, RHC right heart catheterization, SD standard deviation, US United States, WHO World Health Organization
6MWD

Thirteen studies evaluated the relationship between 6MWD and death \((n = 10)\), death or lung transplant \((n = 3)\), PAH-related death or hospitalization \((n = 1)\), and risk of experiencing a costly event indicative of clinical worsening \((n = 2)\) (Table 4).

6MWD and Risk of Death

Risk of death was increased among patients with 6MWD that was shorter \([2, 36]\), below the median \((< 380 \text{ m}) [2]\), or in lower quartiles at baseline (reference: Q1 ≤ 380 m) [37]. Specifically, risk of death at 1 year was increased among patients with shorter 6MWD \([38]\) or 6MWD < 165 m at baseline \([38, 39]\) and decreased among patients with 6MWD ≥ 440 m at baseline [39]. Risk of death within 2 years was increased among patients with 6MWD that was shorter or in lower quartiles at baseline [40]. Further, 6MWD ≤ 250 m at baseline was independently associated with an increased risk of patients dying within 2 years relative to patients surviving ≥ 5 years [41]. Risk of death was also increased at 3 years [42] and 4 years [43] among patients with shorter 6MWD at baseline.

At follow-up, risk of death was increased among patients with 6MWD that was shorter [2], in lower quartiles (reference: Q1 ≤ 348 m) [37], or below the median (defined as ≤ 400 m [37] or < 418 m [2]). Within 1 year, risk of death was increased among patients with 6MWD that was < 165 m [38]. Risk of death within 2 years was increased among patients with 6MWD that was shorter or in lower quartiles at 12-week assessment [40]. At 3 years, risk of death was increased among patients with smaller improvements in 6MWD between baseline and the 12-week follow-up compared with patients with ≥ 20 m increases in 6MWD [44].

6MWD and Risk of Death or Lung Transplant

Risk of death or lung transplant was increased among patients with 6MWD that was shorter [34, 45] or below cutoff at baseline \((≤ 342 \text{ m}) [34]\). Risk of death or lung transplant at 5 years was increased among patients with shorter baseline 6MWD [46].

At follow-up, risk of death or lung transplant was higher among patients with 6MWD that was shorter [45] or declined ≥ 35 m or ≥ 8% [34].

6MWD and Risk of PAH-Related Death or Hospitalization

Risk of PAH-related death or hospitalization was increased among patients with 6MWD in lower quartiles at baseline (reference: Q1 ≤ 300 m) [37]. At follow-up, risk was increased among patients with 6MWD in lower quartiles or below the median \((≤ 400 \text{ m}) [37]\).

6MWD and Risk of Clinical Worsening

Risk of clinical worsening increased among patients with 6MWD that was shorter [2, 34] or ≤ 342 m at baseline [34]. Risk was higher among patients with shorter [2] or decreasing 6MWD at follow-up [2, 34].

FC

Sixteen studies evaluated the relationship between FC and death \((n = 9)\), death or lung transplant \((n = 4)\), experiencing a costly event indicative of clinical worsening \((n = 3)\), using health care resources \((n = 2)\), and incurring health care costs \((n = 1)\) (Table 4).

FC and Risk of Death

Patients with an increased risk of death at follow-up had more severe baseline FC (III/IV) [2, 36, 47], with highest risk of death within 1 year specifically among FC IV patients [39]. Further, FC IV symptomatology at baseline was independently associated with an increased likelihood of reduced survival (dying within 2 years) in univariate and multivariate analysis excluding initial PAH therapy [41]. Risk of death within 3 years was significantly higher for patients with more severe FC (III/IV) at baseline [42, 44]. Within 5 years, risk of death was higher for FC III or IV patients at baseline and increased 69% per class [48].

Risk of death was also predicted by more severe FC (III/IV) at follow-up [2]. Patients who improved at least one FC from baseline to follow-up had a similar risk of death compared with patients whose FC did not improve, but patients who improved from FC III/IV to I/II at follow-up had a reduced risk of death compared with patients who remained in FC III/IV at both time points [2]. Risk of death at 3 years was higher for patients whose FC worsened or remained unchanged compared with those whose FC improved within 1 year of enrollment [49].

FC and Risk of Death or Lung Transplant

For the combined endpoint of risk of death or lung transplant, risk was higher among patients with more severe FC (III/IV) at baseline in studies examining FC [35, 45]. Risk of death or lung transplant within 5 years was higher for patients with more severe FC (III/IV) at baseline [46].

Risk of death or lung transplant was also predicted by more severe FC (III/IV) [45] at follow-up and changes in FC between baseline and follow-up. Risk of death or lung transplant within 5 years was increased for patients whose
| References         | Noninvasive endpoint | Outcome                                                                 | Observed relationship* |
|--------------------|----------------------|--------------------------------------------------------------------------|-------------------------|
| Souza et al. [37]  | 6MWD                 | PAH-related death or hospitalization over a maximum of 36 months from follow-up (median treatment duration: 2.2 years) | Patients with 6MWD in lower quartiles at baseline (reference: Q1 ≤ 300 m) or 6-month follow-up (reference: Q1 ≤ 348 m) had an increased risk of PAH-related death or hospitalization. Patients with 6MWD below the median (≤ 400 m) at 6-month follow-up had an increased risk of PAH-related death or hospitalization. Patients with a 6MWD ≤ 400 m at 6 months had a similarly poor long-term outcome regardless of whether their baseline 6MWD was > 400 m or ≤ 400 m. |
| Weatherald et al. [45] | 6MWD             | All-cause death over a maximum of 36 months from follow-up (median treatment duration: 2.2 years) | Patients with 6MWD in lower quartiles at baseline (reference: Q1 ≤ 300 m) or 6-month follow-up (reference: Q1 ≤ 348 m) had an increased risk of all-cause death. Patients with a 6MWD ≤ 400 m at 6 months had a similarly poor long-term outcome regardless of whether their baseline 6MWD was > 400 m or ≤ 400 m. |
| Zelniker et al. [38] | 6MWD             | Death at 1 year                                                          | Patients with shorter 6MWD or 6MWD below a cutoff of < 165 m at baseline have an increased risk of death at 1 year; similar findings at follow-up. Patients with decreasing 6MWD between baseline and follow-up had an increased risk of death at 1 year. |
| Ghofrani et al. [2]  | 6MWD               | Death                                                                    | Patients with shorter 6MWD or 6MWD less than the median (< 380 m) at baseline had a significantly increased risk of death in bivariate Cox proportional hazards models; similar findings for shorter 6MWD or 6MWD less than the median (< 418 m) at follow-up in univariate analysis. |
|                    | 6MWD               | Clinical worsening (see Table 3 for definition)                          | Patients with shorter 6MWD at baseline or declining 6MWD between baseline and follow-up had significantly increased risk of clinical worsening in bivariate Cox proportional hazards models; similar findings for shorter and declining 6MWD at follow-up in univariate analysis. |
| References          | Noninvasive endpoint | Outcome                                      | Observed relationship*                                                                 |
|---------------------|----------------------|----------------------------------------------|----------------------------------------------------------------------------------------|
| Huang et al. [34]   | 6MWD                 | Death or lung transplant                     | Patients with shorter 6MWD or 6MWD ≤ 342 m at baseline had an increased risk of death or lung transplant; similar findings for declines in 6MWD ≥ 35 m or ≥ 8% at 6-month follow-up |
|                     | 6MWD                 | Clinical worsening (see Table 3 for definition) | Patients with shorter 6MWD or 6MWD ≤ 342 m at baseline had an increased risk of clinical worsening; similar findings for declines in 6MWD ≥ 35 m or ≥ 8% prediction US (American reference equation) or ≥ 6% prediction CAN (Canadian reference equation) at 6-month follow-up |
| Ozpelit et al. [36] | 6MWD                 | Death at follow-upd                         | Patients with shorter 6MWD at baseline had a greater risk of death at follow-upd in univariate analysis |
| Zelniker et al. [43]| 6MWD                 | Death at 4 years                             | Patients with lower 6MWD at baseline had a greater risk of death at 4 years               |
| Fritz et al. [40]   | 6MWD                 | Death at 2 years                             | Patients with shorter baseline 6MWD or in the lower quartiles of 6MWD had a greater risk of death at 2 years; similar findings for 6MWD at 12 weeks |
| Batal et al. [41]   | 6MWD                 | Death within 2 years                         | 6MWD < 250 m at baseline was independently associated with an increased risk of patients dying within 2 years relative to patients surviving ≥ 5 years |
| Nickel et al. [46]  | 6MWD                 | Death or lung transplant within 5 years     | Patients with shorter baseline 6MWD had a higher risk of death or lung transplant in univariate and multivariate analysis |
| Benza et al. [44]   | 6MWD                 | Death at 3 years                             | Patients with smaller improvements in 6MWD between baseline and 12-week follow-up had an increased risk of mortality at 3 years compared with patients with ≥ 20 m increases in 6MWD |
| Benza et al. [39]   | 6MWD                 | Death at 1 year                              | Patients with a baseline 6MWD < 165 m have a significantly increased risk of death at 1 year, while patients with baseline 6MWD ≥ 440 m had a significantly lower risk of death at 1 year |
| Humbert et al. [42] | 6MWD                 | Death within 3 years                         | Patients with shorter 6MWD at baseline have a higher risk of death in individual Cox proportional hazards analysis and a multivariable Cox proportional hazards model |
| Snipelisky et al. [47]| NYHA                | Death at follow-upf                         | Patients with more severe NYHA FC at baseline had an increased risk of death              |
Table 4 (continued)

| References       | Noninvasive endpoint | Outcome                                      | Observed relationship*                                                                 |
|------------------|----------------------|----------------------------------------------|----------------------------------------------------------------------------------------|
| Weatherald et al. [45] | NYHA     | Death or lung transplant                      | Patients with more severe baseline NYHA FC (III/IV) had an increased risk of death or lung transplant over a median follow-up of 2.8 years (IQR: 1.1–4.6) in univariable and multivariable analyses. At first follow-up (median time to first follow-up right heart catheterization was 4.6 months [IQR: 3.7–7.8]), patients with more severe NYHA FC (III/IV) had an increased risk of death or lung transplant over a median follow-up of 2.8 years (IQR: 1.1–4.6) in univariable and multivariable analyses. |
| Dufour et al. [6] | WHO      | Health care resource utilization               | Patients with WHO FC IV had significantly more inpatient admissions, longer average lengths of stay, and more emergency department visits than other FC subgroups. Mean total health care costs for patients with PAH were higher than costs for a Centers for Medicare and Medicaid Services managed care control group and increased with more severe FC. Patients in WHO FC IV have the highest costs. |
| Tang et al. [35] | WHO      | All-cause death or lung transplant            | Patients with more severe WHO FC (III/IV) had an increased risk of all-cause death or lung transplant. Patients with more severe WHO FC (III/IV) had increased risk of clinical worsening. |
| Ghofrani et al. [2] | WHO      | Death                                        | Patients with poor baseline WHO FC (III/IV) had significantly increased risk of death in a bivariate Cox proportional hazards model; similar findings for follow-up FC in univariate analysis. Patients who improved at least one WHO FC from baseline to follow-up had a similar risk of death compared with patients whose FC did not improve, but patients who improved from WHO FC III/IV to I/II at follow-up had a reduced risk of death compared with patients who remained in WHO FC III/IV at both timepoints. Clinical worsening (see Table 3 for definition) | Patients with poor baseline WHO FC (III/IV) or worsened FC (changing from I/II to III/IV between baseline and follow-up) had a significantly greater risk of clinical worsening in a bivariate Cox proportional hazards model; similar findings for follow-up FC in univariate analysis. |
| Huang et al. [34] | WHO      | Clinical worsening (see Table 3 for definition) | More severe baseline WHO FC (III/IV) was associated with an increased risk of clinical worsening. |
| Ozpelit et al. [36] | NYHA     | Death at follow-up                            | Patients with more severe NYHA FC (III/IV) at baseline had an increased risk of death at follow-up in univariable and multivariate analysis. |
| References    | Noninvasive endpoint | Outcome                  | Observed relationship* |
|--------------|----------------------|--------------------------|-------------------------|
| Ehlken et al. [53] | WHO                  | Health care resource utilization | Compared with patients who received medical therapy alone, patients with severe PAH who received exercise training plus medical therapy reduced their WHO FC, which was associated with less health care resource utilization |
| Barst et al. [49] | NYHA/WHO             | Death at 3 years         | Compared with those whose FC improved within 1 year of enrollment, patients whose NYHA/WHO FC worsened and those whose FC remained unchanged had an increased risk of death within 3 years. This trend was stronger in a subanalysis of patients with only idiopathic/familial PAH |
| Tiede et al. [50] | WHO                  | Death or lung transplant | At follow-up (16 weeks ± 2.5 SDs; range: 4–29), patients with stable or deteriorated WHO FC had higher risk of death or lung transplant within 7 years (mean follow-up: 4.7 years) compared with patients whose FC improved in univariate Cox regression analysis |
| Batal et al. [41] | WHO                  | Death within 2 years     | Baseline WHO FC IV was independently associated with an increased likelihood of patients dying within 2 years relative to patients surviving ≥ 5 years in univariate and multivariate analysis excluding initial PAH therapy |
| Nickel et al. [46] | WHO                  | Death or lung transplant within 5 years | Patients with more severe WHO FC (III/IV) at baseline had an increased risk of death or lung transplant in univariate analysis. Patients whose FC remained IV or III or increased to III/IV during follow-up had a higher risk of lung transplant and death compared to patients remaining stable at FC I/II and patients who improved from FC III/IV to II in multivariate analysis. |
| Benza et al. [44] | NYHA                 | Death at 3 years         | Patients with NYHA FC IV had an increased risk of death at 3 years compared with patients with FC III and FC II. Patients with NYHA FC II had a reduced risk of death at 3 years compared with patients with NYHA FC III |
| Kane et al. [48]  | WHO                  | Death within 5 years     | Patients with more severe WHO FC (III/IV) at baseline have an increased risk of death within 5 years, with risk increasing by 69% per class |
| Benza et al. [39] | NYHA/WHO             | Death at 1 year          | At baseline, patients with NYHA/WHO FC IV had the highest risk of death at 1-year, followed by patients with NYHA/WHO FC III. Patients with modified NYHA/WHO FC-I at baseline had a significantly reduced risk of death at 1 year |
| Humbert et al. [42] | WHO                  | Death within 3 years     | Patients with WHO FC I/II at baseline have a significantly lower risk of death in individual Cox proportional hazards analysis |

**Table 4 (continued)**
| References          | Noninvasive endpoint | Outcome         | Observed relationship*                                                                                                                                                                                                 |
|---------------------|----------------------|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Frantz et al. [52]  | BNP                  | Death at 5 years | Compared with patients with lower baseline levels (≤340 pg/mL), patients with higher baseline levels of BNP (>340 pg/mL) had a greater risk of death at 5 years. Effect of change to BNP between baseline and 1-year follow-up on risk of death at 5 years: Greatest risk: patients whose BNP remains high (>340 pg/mL). Second greatest risk: patients with increasing BNP. Third greatest risk: patients whose BNP decreases. Lowest risk: patients whose BNP remained low (≤340 pg/mL). |
| Tang et al. [35]    | NT-proBNP            | All-cause death or lung transplant | Patients with higher NT-proBNP had an increased risk of death or lung transplant. The optimal cutoff value for NT-proBNP for predicting all-cause death or lung transplant was 1,105.5 pg/mL. Patients with higher NT-proBNP had an increased risk of clinical worsening. |
| Ghofrani et al. [2] | NT-proBNP            | Death            | Patients with NT-proBNP higher or greater than the median (≥467 pg/mL) at baseline or increased NT-proBNP between baseline and follow-up had significantly increased risk of death in a bivariate Cox proportional hazards model; similar findings for NT-proBNP higher or greater than the median (≥268 pg/mL) at follow-up in univariate analysis. Patients with NT-proBNP higher or greater than the median (≥467 pg/mL) at baseline or increased NT-proBNP between baseline and follow-up had significantly increased risk of clinical worsening in a bivariate Cox proportional hazards model; similar findings for NT-proBNP higher or greater than the median (≥268 pg/mL) at follow-up in univariate analysis. Time to first event was predicted by baseline NT-proBNP (0.91; 95% CI 0.88–0.94; P < 0.0001), change from baseline in NT-proBNP (0.90; 95% CI 0.85–0.95; P < 0.0001), and NT-proBNP at follow-up (0.91; 95% CI, 0.88–0.94; P < 0.0001). |
| Ozpelit et al. [36] | BNP                  | Death at follow-up | Patients with higher BNP at baseline have an increased risk of death at follow-up in univariate and multivariate analysis. |
| Zelniker et al. [43]| NT-proBNP            | Death at 4 years | Patients with NT-proBNP > 704.5 pg/mL at baseline have a greater risk of death at 4 years. |
| References          | Noninvasive endpoint | Outcome                                      | Observed relationship*                                                                 |
|---------------------|----------------------|----------------------------------------------|----------------------------------------------------------------------------------------|
| Fritz et al. [40]   | BNP                  | Death at 2 years                             | Higher baseline BNP was associated with a greater risk of death over 2 years; similar findings for BNP at 12 weeks |
| Nickel et al. [46]  | NT-proBNP            | Death or lung transplant within 5 years      | Patients with elevated NT-proBNP at baseline or whose NT-proBNP remained high or increased to ≥ 1,800 ng/L from baseline to follow-up had increased risk of lung transplant and death at 1, 3, and 5 years in univariate and multivariate analysis, compared with patients whose NT-proBNP was low and with patients whose NT-proBNP remained low or decreased |
| Kane et al. [48]    | FC                   | Death within 5 years                         | Patients with more severe WHO FC (III/IV) at baseline have an increased risk of death within 5 years, with risk increasing by 69% per class |
| Mauritz et al. [51] | NT-proBNP            | Death at follow-up                           | Patients with higher NT-proBNP at baseline had a greater risk of death at follow-up |
| Benza et al. [39]   | BNP                  | Death at 1 year                              | At baseline, patients with BNP higher than threshold (>180 pg/mL) have a significantly higher risk of death at 1 year, while patients with BNP lower than threshold (< 50 pg/mL) have a significantly lower risk of death at 1 year |

**Risk groups**

| References          | Noninvasive endpoint | Outcome                                      | Observed relationship*                                                                 |
|---------------------|----------------------|----------------------------------------------|----------------------------------------------------------------------------------------|
| Boucly et al. [54]  | 6MWD, FC (WHO), and BNP/NT-proBNP | Death or lung transplant at follow-up | Patients who achieved fewer low-risk criteria (including 6MWD > 440 m and FC I/II) have a higher risk of death or lung transplant In a subgroup analysis at first re-evaluation where BNP < 50 ng/L or NT-proBNP < 300 ng/L was added to the univariate and multivariate analyses, the number of noninvasive low-risk criteria achieved (WHO/NYHA FC I/II, 6MWD > 440 m, and BNP < 50 ng/L or NT-proBNP < 300 ng/L) significantly predicted lower risk of lung transplant or death; hemodynamic low-risk criteria were no longer significant in this model |
| Hoepner et al. [12] | 6MWD, FC (WHO), and BNP/NT-proBNP | Death within 5 years                          | 6MWD, FC (WHO), and BNP/NT-proBNP were the top factors determining a patient's risk of mortality within 5 years in an analysis that also considered right atrial pressure, cardiac index, and mixed venous oxygen saturation as risk factors |
### Table 4 (continued)

| References            | Noninvasive endpoint     | Outcome               | Observed relationship* |
|-----------------------|--------------------------|-----------------------|------------------------|
| Kylhammar et al. [55] | 6MWD, FC (WHO), and NT-proBNP | Death within 5 years | Patients in the high-risk group at baseline had the greatest risk of death within 5 years, followed by patients in the intermediate risk group, with patients in the low-risk group with the lowest risk of death at those timepoints; similar findings for risk groups at follow-up. Patients with a lower proportion of variables at “low risk” at follow-up had a greater risk of death within 5 years than patients with stable intermediate risk or high risk or who worsened to intermediate risk or high risk between baseline and follow-up. Patients with stable low risk or who improved to low risk between baseline and follow-up had a greater risk of death within 5 years compared with patients with stable low risk or who improved to low risk between baseline and follow-up. |

6MWD 6-minute walk distance, BNP brain natriuretic peptide, CI confidence interval, FC functional class, IQR interquartile range, NT-proBNP N-terminal cleavage product of its prohormone, NYHA New York Heart Association, PAH pulmonary arterial hypertension, Q1 first quartile, SD standard deviation, US United States, WHO World Health Organization

*Median time between the 2 6MWTs was 14.0 weeks (IQR 7.7–26.1)

*Over a median of 34 months (IQR 16–56)

*Median: 4.4 months [IQR 3.6–6.4], maximum: 1 year

*Followed up for mean ± SD 36.8 ± 23.6 months

*Median follow-up was 38 months (IQR 25–70)

*Mean ± SD follow-up was 4.53 ± 2.64 years

*Median ± SD follow-up was 41 ± 15 months (maximum: 66 months)

*b 3–12 months after initiation of PAH-targeted therapy

*Median follow-up of 3.2 years (IQR 1.3–5.0)

*Mean ± SD follow-up period of 38 ± 23 months

*Patient risk was assessed according to the number of low-risk criteria achieved, including the following: WHO/NYHA FC I-II, 6MWD > 440 m, right atrial pressure < 8 mm Hg, and cardiac index ≥ 2.5 min⁻¹ m⁻²; risk for a subset of patients with BNP or NT-proBNP measurements available at follow-up (n = 630) was considered in univariate and multivariate analysis where BNP < 50 ng/L or NT-proBNP < 300 ng/L was added as an additional noninvasive low-risk criterion

*Follow-up was 27 (11–51) months

*mMedian time from baseline to first follow-up was 4 months (IQR 3–5)
FC remained III or IV or increased to III/IV during follow-up compared with patients who remained at FC I/II and patients who improved from FC III/IV to I/II [46]. Within 7 years, risk of death or lung transplant similarly increased for patients with stable or deteriorated FC compared with patients whose FC improved [50].

**FC and Risk of Clinical Worsening**

Risk of clinical worsening was increased among patients with more severe FC (III/IV) at baseline [2, 34, 35]. More severe FC (III/IV) at follow-up or FC that worsened (from I/II to III/IV) between baseline and follow-up also predicted clinical worsening [2].

**BNP/NT-proBNP**

Nine studies evaluated the relationship between BNP/NT-proBNP and risk of death (n = 7), experiencing a costly event indicative of clinical worsening (n = 2), and death or lung transplant (n = 2) (Table 4). The frequency of use of BNP (four studies) and NT-proBNP (five studies) was similar in the literature, with no clear temporal differences by year of publication or study start date.

**BNP/NT-proBNP and Risk of Death**

Risk of death was increased for patients with higher BNP [36] or NT-proBNP at baseline [2, 51] or NT-proBNP above the median (≥ 467 pg/mL) [2] or cutoff (>1256 pg/mL) at baseline [51]. Risk of death at 1 year was increased for patients with BNP higher than the threshold (> 180 pg/mL) at baseline [39]. Risk of death at 2 years was increased among patients with higher BNP at baseline [40]. At 4 years, risk of death was increased among patients with NT-proBNP > 704.5 pg/mL at baseline [43]. Increased risk of death at 5 years was associated with baseline levels of BNP > 340 pg/mL [52].

Risk of death also increased for patients whose NT-proBNP was higher [2], greater than the median (≥ 268 pg/mL) [2], or increased between baseline and follow-up [2, 51]. Risk of death at 2 years, in particular, was increased among patients with elevated BNP at the week 12 assessment [40]. Risk of death at 5 years was highest among patients whose BNP remained high (> 340 pg/mL), followed by patients with increased BNP at 1 year of follow-up; patients whose BNP decreased or remained low (≤ 340 pg/mL) at 1 year of follow-up had the lowest risk [52].

**NT-proBNP and Risk of Death or Lung Transplant**

Risk of death or lung transplant was increased for patients with elevated NT-proBNP at baseline [35, 46]. An optimal cutoff of NT-proBNP > 1105.5 pg/mL at baseline predicted risk of all-cause death or lung transplant [35]. Risk of death at 1, 3, and 5 years was increased among patients whose NT-proBNP remained high or increased to ≥ 1800 ng/L at follow-up [46].

**NT-proBNP and Risk of Clinical Worsening**

Risk of clinical worsening was increased among patients with NT-proBNP that was elevated [2, 35] or greater than the median (≥ 467 pg/mL) at baseline [2]. Risk of clinical worsening was also increased among patients with elevated or increased NT-proBNP at follow-up [2].

**FC and Economic Outcomes**

Mean total health care costs for patients with PAH were higher than costs for a Centers for Medicare and Medicaid Services managed care control group and increased with more severe baseline FC, with patients in FC IV having the highest costs [6]. Health care resource utilization, including inpatient admissions, longer average lengths of stay, and emergency department visits, was also greater for patients with FC IV than other FC subgroups [6]. In another study, patients with severe PAH who received medical therapy alone were more likely to have more severe FC (III/IV), which was associated with greater health care resource utilization compared with patients who received exercise training plus medical therapy [53].

**6MWD, FC, and BNP/NT-proBNP Risk Groups**

Three studies evaluated the relationship between risk group and death within 5 years (n = 2) and death or lung transplant (n = 1) (Table 4). The 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines were used to stratify patients as low, intermediate, or high risk [12, 54, 55]. All three studies considered FC and 6MWD when determining risk [12, 54, 55] (Table 4). Two considered BNP/NT-proBNP in the primary determination of risk [12, 55], while one study considered the additive value of BNP < 50 ng L⁻¹ or NT-proBNP < 300 ng L⁻¹ low-risk criteria [54]. Additional factors considered in determining risk included right atrial pressure, cardiac index, mixed venous oxygen saturation [12, 54, 55], right atrial area, and pericardial effusion [55]. Risk was determined by a mean score calculated using the sum of the grades assigned to each risk factor from 1 (low risk) to 3 (high risk) and dividing by the total number of risk factors [12, 55] and by the number of low-risk criteria present at baseline and re-evaluation (FC I-II, 6MWD > 440 m, right atrial pressure < 8 mm Hg and cardiac index ≥ 2.5 min⁻¹ m⁻²) [54].

 Springer
Risk Groups and Risk of Death

Risk of death within 5 years was increased among patients with a higher proportion of “high-risk” variables at both baseline and follow-up, determined with the inclusion of 6MWD, FC, and NT-proBNP [55]. 6MWD followed by FC and BNP/NT-proBNP most strongly correlated with a patient’s risk of death within 5 years [12].

Risk Groups and Risk of Death or Lung Transplant

At baseline, all four low-risk criteria significantly predicted risk of death or lung transplant in univariable analysis; 6MWD > 440 m was the only low-risk criterion remaining significant in multivariable analysis [54]. At first re-evaluation, all four low-risk criteria significantly predicted risk of death or lung transplant in univariable analysis; 6MWD > 440 m was the only low-risk criterion remaining significant in multivariable analysis [54]. Outcomes were similar for patients who had an increase in the number of low-risk criteria achieved between baseline and first re-evaluation (< 3 to having 3–4) and those who had 3–4 low-risk variables at both time points. Patients with less than three low-risk criteria at both baseline and first revaluation had the greatest risk of death or lung transplant; for patients with zero low-risk variables at follow-up, transplant-free survival was worse for those with two high-risk variables than for those with one. In the subgroup of patients who had all three noninvasive measurements at follow-up, risk of death or lung transplant was significantly lower for patients who achieved one or more low-risk criteria (FC I-II, 6MWD > 440 m, BNP < 50 ng L⁻¹); in this multivariable model, hemodynamic low-risk criteria (right atrial pressure < 8 mm Hg and cardiac index ≥ 2.5 min⁻¹ m⁻²) were no longer significant predictors of transplant-free survival [54].

Discussion

This review provides support for 6MWD, FC, and BNP/NT-proBNP as correlates of risk of long-term health outcomes (e.g., mortality and clinical worsening), costly events (e.g., lung transplants or hospitalization), and economic outcomes (e.g., costs and resource utilization) in PAH. Relative to patients with longer or increased 6MWD, patients with shorter or decreased 6MWD have a higher risk of death and experiencing costly events indicative of clinical worsening, such as hospitalization or lung transplant. Compared to patients with more favorable (I or II) or improved FC, patients with poorer (III or IV) or declined FC consume greater health care resources, incur higher health care costs, and are at an increased risk of death and clinical worsening. Patients with elevated or increased BNP/NT-proBNP have a higher risk of death and clinical worsening relative to patients with lower or decreased BNP/NT-proBNP. In addition, patients classified into more severe risk groups, determined by multiple noninvasive endpoints (e.g., 6MWD, FC, and BNP/NT-proBNP), have an increased risk of death and lung transplant.

These findings are important considering the current shift from using these noninvasive measures as primary and secondary endpoints in PAH clinical trials to evaluating mortality and clinical worsening in clinical trials. A related review has also concluded that 6MWD and FC are clinically meaningful trial endpoints associated with outcomes in patients with PAH and CTEPH [16]. While mortality and clinical worsening are robust and valuable long-term endpoints in clinical trials, 6MWD, FC, and BNP/NT-proBNP are universally defined and recognized, enabling comparisons of treatment efficacy across trials using these endpoints. 6MWD and FC are already being included in the composite endpoint of clinical worsening in many trials and in risk calculators such as REVEAL 2.0 [13]. BNP/NT-proBNP is also included in risk calculators [13] and is a prominent biomarker used in clinical management [56, 57] as well as part of the multiparametric risk assessment approach outlined in guidelines [58]. These noninvasive endpoints are simpler and more inexpensive to assess relative to event-based endpoints [14]. For instance, morbidity and mortality event trials require a large number of subjects in order to demonstrate effects even as early as 1 year [59, 60]. Looking to the future, consideration should be given to including 6MWD, FC, and BNP/NT-proBNP in the assessment of time to clinical improvement, a new endpoint proposed at the recent 6th World Symposium on Pulmonary Hypertension [61].

Conclusions from the present review should be considered with caution because no pooled analysis was performed to evaluate the observed relationships between the noninvasive endpoints and long-term outcomes for statistical significance. Previous meta-analyses and pooled analyses for 6MWD have found no correlation between 6MWD and mortality [21] and clinical events [22] or only modest validity for 6MWD as a surrogate endpoint [18]. Given that the majority of studies evaluating 6MWD included in this review were published after these studies were conducted (10 of 13 studies), an updated analysis is needed in order to confirm our observations. In addition, the paucity of literature evaluating health care resource utilization and costs in PAH limits the ability to draw conclusions on the predictive nature of noninvasive endpoints in terms of economic outcomes. However, given what is known about the relationships between noninvasive endpoints and events, such as hospitalization and lung transplant, the economic impact may be extrapolated using...
existing data on the costs of those events. Further, our review did not consider the predictive value of additional variables that are considered in risk assessments such as cardiopulmonary exercise testing, imaging (e.g., echocardiogram, cardiac magnetic resonance imaging), hemodynamics, and right heart catheterization [13, 56]. While these variables are important, our review focused on the noninvasive endpoints most commonly used in clinical trials and risk assessments that are most efficient and inexpensive to assess.

Conclusions

Mortality and clinical worsening will continue to be valuable endpoints in assessing treatment efficacy and safety in PAH; however, these endpoints require lengthy follow-up and cannot be applied in clinical settings where risk reduction is the goal of treatment. Further, differing definitions used for clinical worsening across trials limit the ability of stakeholders to compare treatment efficacy. 6MWD, FC, and BNP/NT-proBNP are universally defined, low-cost, efficient, noninvasive endpoints that correlate with long-term health and economic outcomes in patients with PAH. Collectively, they are important components of risk assessments and will remain beneficial in the clinic to guide treatment decisions. Future research should meta-analytically examine the relationships between these noninvasive endpoints and long-term outcomes for statistical significance. Additional studies are needed examining the relationship between 6MWD, FC, and BNP/NT-proBNP and economic outcomes and the potential utility of 6MWD, FC, and BNP/NT-proBNP as a composite endpoint assessing risk.

Funding United therapeutics supported this research.

Compliance with Ethical Standards

Conflict of interest Samantha Wronski and Margaret Mordin are employees of RTI Health Solutions. Kim Kelley is business owner of Rx Trusted Advisors, PLLC which works with life science and futurist groups, along with peer to peer learning, pipeline strategy sessions. And additional work advising in high cost pharmacy and medical cases. Previous Director of Pharmacy for BlueCross and BlueShield of Arizona. Groups and organizations I have worked directly or indirectly with or own stock include; Rx Worldwide Meetings, Navigant Life Sciences, Amgen, Novartis, UCB, Gerson Lehrman Group Council, Lilly, United Therapeutics Corporation, CB Partner, McCann Health, ClearView Health Partners, Parallax Life Sciences, Insmed, Integrated Healthcare Management, Business Talent Group, Evidera, and River West Meeting Associates. Dr. Angiulo is on the speaker’s bureau and advisory board for United Therapeutics. Peter Classi is an employee and minor shareholder in United Therapeutics Corporation. Eric Shen is an employee of United Therapeutics Corporation. Scott Manaker is a Grand Rounds speaker, lecturer, consultant, and expert witness on documentation, coding, billing, and reimbursement to hospitals, physicians, departments, practice groups, professional societies, insurers, and attorneys (defense, plaintiff “qui tam”, US Attorneys General, and the Office of the Inspector General). Consultant to Apnecure, Aetna, Pfizer, Novartis and Johnson & Johnson. Expert witness in workers’ compensation and in medical negligence matters. Chair, Practice Expense Subcommittee of the American Medical Association/Specialty Society Relative Value Update Committee (RUC). Member, Hospital Outpatient Panel, a federal advisory commission to the Center for Medicare/Medicaid Services (CMS) for the Outpatient Hospital Prospective Payment System. Stock held in 3M; and (by spouse) in Pfizer, Johnson & Johnson. Director of ACCP Enterprises, a wholly owned for-profit subsidiary of ACCP. Section Editor (Critical Care), UpToDate. Associate Editor, CHEST Journal. Trustee, National Board for Respiratory Care.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Frost AE, Badesch DB, Barst RJ et al (2011) The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US Contemporary Registries. Chest 139(1):128–137

2. Ghofrani H, Grimminger F, Grüng E et al (2016) Predictors of long-term outcomes in patients treated with riociguat for pulmonary arterial hypertension: data from the PATENT-2 open-label, randomised, long-term extension trial. Lancet Respir Med 4(5):361–371

3. Lan NSH, Massam BD, Kulkarni SS, Lang CC (2018) Pulmonary arterial hypertension: pathophysiology and treatment. Diseases 6(2):38

4. Burger CD, Ghandour M, Padmanabhan Menon D, Helmi H, Benza RL (2017) Early intervention in the management of pulmonary arterial hypertension: clinical and economic outcomes. Clinicoecon Outcomes Res 9:731–739

5. Burke JP, Hunsche E, Regulier E, Nagao M, Buzinec P, Drake Iii W (2015) Characterizing pulmonary hypertension-related hospitalization costs among Medicare Advantage or commercially insured patients with pulmonary arterial hypertension: a retrospective database study. Am J Manag Care 21(3 Suppl):s47–58

6. Dufour R, Pruett J, Hu N et al (2017) Healthcare resource utilization and costs for patients with pulmonary arterial hypertension: real-world documentation of functional class. J Med Econ 20(11):1178–1186

7. Lajoie AC, Bonnet S, Lacasse Y, Lega J-C, Provencher S (2018) Interpreting risk reduction in clinical trials for pulmonary arterial hypertension. Eur Respir Rev 27(148):180020

8. Galile H, Channick RN, Frantz RP et al (2019) Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J 53(1):1801889

9. Parikh KS, Rajagopal S, Arges K et al (2015) Use of outcome measures in pulmonary hypertension clinical trials. Am Heart J 170(3):419–429.e413

10. Rainer A, Humbert M (2016) Risk assessment in pulmonary arterial hypertension. Eur Respir Rev 25(142):390–398

11. Galile H, Humbert M, Vuchery J-L et al (2015) 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 46(4):903
12. Hoepf MM, Kramer T, Pan Z et al (2017) Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary arterial hypertension guidelines risk stratification model. Eur Respir J 50(2):1700740

13. Benza RL, Gomberg-Maitland M, Elliott CG et al (2019) Predicting survival in patients with pulmonary arterial hypertension: the REVEAL risk score calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. Chest 156:323–337

14. Snow JL, Kawut SM (2007) Surrogate endpoints in pulmonary arterial hypertension: the response to therapy. Clin Chest Med 28(1):75–89

15. Zamanian RT, Kudelko KT, Sung YK, Perez VdJ, Liu J, Spierekkoetter E (2014) Current clinical management of pulmonary arterial hypertension. Circ Res 115(1):131–147

16. Divers C, Platt D, Wang E, Liu J, Lingohr-Smith M, Mathai SC (2015) 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. J Manag Care Spec Pharm 23(1):92–104

17. Farber HW, Miller DP, McGoone MD, Frost AE, Benton WW, Benza RL (2015) Predicting outcomes in pulmonary arterial hypertension based on the 6-minute walk distance. J Heart Lung Transplant 34(3):362–368

18. Gabler NB, French B, Strom BL, Palevsky HI, Taichman DB, Kawut SM, Halpern SD (2012) Validation of 6-minute walk distance as a surrogate endpoint in pulmonary arterial hypertension trials. Circulation 126(3):349–356

19. Gomberg-Maitland M, Bull TM, Saggari R et al (2013) New trial designs and potential therapies for pulmonary artery hypertension. J Am Coll Cardiol 62(25 Suppl):D82–D91

20. Hill NS, Cawley MJ, Heggen-Peay CL (2016) New therapeutic paradigms and guidelines in the management of pulmonary arterial hypertension. J Manag Care Spec Pharm 22(3-a Suppl):x3–x21

21. Macchia A, Marchioli R, Marfisi R, Scano M, Levantesi G, Tavazzi L, Tognoni G (2007) A meta-analysis of trials of pulmonary hypertension: A clinical condition looking for drugs and research methodology. Am Heart J 153(6):1037–1047

22. Savarese G, Paolillo S, Costanzo P et al (2012) Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. J Am Coll Cardiol 60(13):1192–1201

23. Studer SM, Gilkin RJ Jr (2014) Clinical trial designs in PAH: shifting from functional measurements to long-term clinical outcomes. J Am Manag Care 20(6 Suppl):S115–122

24. Vachiery J-L, Yerly P, Huez S (2012) How to detect disease progression in pulmonary arterial hypertension. Eur Respir Rev 21(123):40–47

25. Waxman AB, Farber HW (2015) Using clinical trial end points to risk stratify patients with pulmonary arterial hypertension. Circulation 132(22):2152–2161

26. Chakinala MM, Barst R (2013) From short-term benefits to long-term outcomes: the evolution of clinical trials in pulmonary arterial hypertension. Pulm Circ 3(1):507–522

27. Galié N, Barberà JA, Frost AE et al (2015) Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 373(9):834–844

28. Sitbon O, Channick R, Chin KM et al (2015) Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med 373(26):2522–2533

29. Pulido T, Adzerikho I, Channick RN et al (2013) Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 369(9):809–818

30. Tapson VF, Sanchez Diaz CJ, Bohns Meyer GM et al (2019) Treatment with oral treprostinil delays time to clinical worsening in patients with pulmonary arterial hypertension - results from FREEDOM-EV. J Heart Lung Transplant 38(4):S94–S95

31. White RJ, Sanchez Diaz CJ, Bohns Meyer GM, Pulido T, Sepulveda P, Wang KY, et al (2019) Treatment with oral treprostinil is associated with improved survival in pulmonary arterial hypertension participants from the FREEDOM-EV study. In: 13th Pulmonary Vascular Research Institute (PVR) Annual World Congress on PVD. Barcelona, Spain

32. White RJ, Jerjes-Sanchez C, Bohns Meyer GM, Pulido T, Sepulveda P, Wang KY et al (2019) Risk scores and risk-based stratification of clinical worsening events in pulmonary arterial hypertension patients treated with oral treprostinil: FREEDOM-EV. Am J Respir Crit Care Med 199(Suppl):A5587–A5587

33. Newman JH, Rich S, Abman SH et al (2017) Enhancing insights into pulmonary vascular disease through a precision medicine approach A joint NHLBI-Cardiovascular Medical Research and Education Fund Workshop report. Am J Respir Crit Care Med 195(12):1661–1670

34. Huang J, Mehta S, Mura M (2015) Early decline in six-minute walk distance from the time of diagnosis predicts clinical worsening in pulmonary arterial hypertension. Respiration 89(5):365–373

35. Tang Y, Luo Q, Liu Z et al (2017) Oxygen uptake efficiency slope predicts poor outcome in patients with idiopathic pulmonary arterial hypertension. J Am Heart Assoc 6(7):e005037

36. Ozpolat E, Akdeniz B, Ozpolat ME et al (2015) Prognostic value of neutrophil-to-lymphocyte ratio in pulmonary arterial hypertension. J Int Med Res 43(5):661–671

37. Souza R, Channick RN, Delcroix M et al (2018) Association between six-minute walk distance and long-term outcomes in patients with pulmonary arterial hypertension: Data from the randomized SERAPHIN trial. PLoS ONE 13(3):e0193226

38. Zelniker TA, Husher D, Vonk-Noordegraaf A et al (2018) The 6MWT as a prognostic tool in pulmonary arterial hypertension: results from the COMPERA registry. Clin Res Cardiol 107:460–470

39. Benza RL, Miller DP, Gomberg-Maitland M et al (2010) Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 122(2):164–172

40. Fritz JS, Blair C, Oudiz RJ et al (2013) Baseline and follow-up 6-min walk distance and brain natriuretic peptide predict 2-year mortality in pulmonary arterial hypertension. Chest 143(2):315–323

41. Batal O, Khatib OF, Dweik RA, Hammel JP, McCarthy K, Minai OA (2012) Comparison of baseline predictors of prognosis in pulmonary arterial hypertension in patients surviving ≤ 2 years and those surviving > 5 years after baseline right-sided cardiac catheterization. Am J Cardiol 109(10):1514–1520

42. Hambert M, Sitbon O, Chaouat A et al (2010) Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation 122(2):156–163

43. Zelniker T, Uhlmann L, Spaich S et al (2015) Novel biomarkers for risk stratification in pulmonary arterial hypertension. ERJ Open Res 1(2):00008

44. Benza RL, Seeger W, McLaughlin VV et al (2011) Long-term effects of inhaled treprostinil in patients with pulmonary arterial hypertension: the Treprostinil Sodium Inhalation Used in PVD. Barcelona, Spain

45. Weatherald J, Bouchy A, Chemla D et al (2018) Prognostic value of follow-up hemodynamic variables after initial management in pulmonary arterial hypertension. Circulation 137(7):693–704
46. Nickel N, Golpon H, Greer M et al (2012) The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. Eur Respir J 39(3):589–596
47. Snipelisky D, Jentzer J, Batal O, Dardari Z, Mathier M (2018) Serum albumin concentration as an independent prognostic indicator in patients with pulmonary arterial hypertension. Clin Cardiol 41:782–787
48. Kane GC, Maradit-Kremers H, Slusser JP, Scott CG, Frantz RP, McGoon MD (2011) Integration of clinical and hemodynamic parameters in the prediction of long-term survival in patients with pulmonary arterial hypertension. Chest 139(6):1285–1293
49. Barst RJ, Chung L, Zamanian RT, Turner M, McGoon MD (2013) Functional class improvement and 3-year survival outcomes in patients with pulmonary arterial hypertension in the REVEAL Registry. Chest 144(1):160–168
50. Tiede H, Sommer N, Milger K et al (2013) Short-term improvement in pulmonary hemodynamics is strongly predictive of long-term survival in patients with pulmonary arterial hypertension. Pulm Circ 3(3):523–532
51. Mauritz GJ, Rizopoulos D, Groepenhoff H et al (2011) Usefulness of serial N-terminal pro-B-type natriuretic peptide measurements for determining prognosis in patients with pulmonary arterial hypertension. Am J Cardiol 108(11):1645–1650
52. Frantz RP, Farber HW, Badesch DB et al (2018) Baseline and serial brain natriuretic peptide level predicts 5-year overall survival in patients with pulmonary arterial hypertension: data from the REVEAL registry. Chest 154:126–135
53. Ehlken N, Verduyn C, Tiede H et al (2014) Economic evaluation of exercise training in patients with pulmonary hypertension. Lung 192(3):359–366
54. Boucly A, Weatherald J, Savale L et al (2017) Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. Eur Respir J 50(2):1700889
55. Kylhammar D, Kjellstrom B, Hjalmarsson C et al (2018) A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. Eur Heart J 39(47):4175–4181
56. Galie N, Humbert M, Vachiery JL et al (2016) 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPedC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 37(1):67–119
57. Iannuzzi GL, D’Alto M, Formisano R, Maniscalco M (2019) Biomarkers in clinical management of pulmonary hypertension: has the emperor no clothes? A call for action. Biomark Med 13(4):235–238
58. Chin KM, Rubin LJ, Channick R et al (2019) Association of N-terminal pro brain natriuretic peptide and long-term outcome in patients with pulmonary arterial hypertension. Circulation 139(21):2440–2450
59. Weatherald J, Boucly A, Sahay S, Humbert M, Sitbon O (2018) The low-risk profile in pulmonary arterial hypertension Time for a paradigm shift to goal-oriented clinical trial endpoints? Am J Respir Crit Care Med 197(7):860–868
60. McLaughlin VV, Hoeper MM, Channick RN et al (2018) Pulmonary arterial hypertension-related morbidity is prognostic for mortality. J Am Coll Cardiol 71(7):752–763
61. Sitbon O, Gomberg-Maitland M, Granton J et al (2019) Clinical trial design and new therapies for pulmonary arterial hypertension. Eur Respir J 53(1):1801908
62. McLaughlin VV, McGoon MD (2006) Pulmonary arterial hypertension. Circulation 114(13):1417–1431
63. Cleveland Clinic (2017) NT-proB-type natriuretic peptide (BNP). https://my.clevelandclinic.org/health/diagnostics/16814-nt-prob-type-natriuretic-peptide-bnp. Accessed 23 Aug 2018.