CONSENSUS STATEMENT

International Society for Heart and Lung Transplantation (ISHLT) Consensus Statement on Risk Stratification in Pulmonary Arterial Hypertension

Sandeep Sahay,[a,1] Scott Visovatti,[b] Adriano R. Tonelli,[c] Nelson Villasmil Hernandez,[d] Eric D. Austin,[e] Roberto Badagliacca,[f] Rolf M.F. Berger,[g] Athénaïs Boucly,[h] Yucheng Chen,[i] Colin Church,[j] Marion Delcroix,[k] Allen D. Everett,[l] Harrison W. Farber,[m] Charles Fauvel,[n] Mardi Gomberg-Maitland,[o] Megan Griffiths,[ad] Francois Haddad,[p] Yuchi Han,[q] Anna Hemnes,[e] Marius M. Hoeper,[r] Manreet K. Kanwar,[s] Daniel Lachant,[t] Sandhya Murthy,[u] Karen M. Olsson,[r] Ioana Preston,[v] Göran Rådegran,[w] Olivier Sitbon,[x] Maria G. Trivieri,[y] Jean-Luc Vachiery,[z] Rebecca Vanderpool,[b] Jason Weatherald,[aa] R. James White,[t] Helen Whitford,[ab] Melisa Wilson,[ac] and Raymond L. Benza,[y,1]

[a]*Division of Pulmonary, Critical Care and Sleep Medicine. Houston Methodist Hospital, Houston, TX;* [b]*Department of Internal Medicine, Division of Cardiovascular Medicine, Davis Heart and Lung Research Institute, The Ohio State University, OH;* [c]*Department of Pulmonary, Allergy and Critical Care Medicine. Respiratory Institute. Cleveland Clinic, Cleveland, OH;* [d]*Department of Medicine. Houston Methodist Academic Institute, Houston, TX;* [e]*Division of Allergy, Immunology, and Pulmonary Medicine, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN;* [f]*Dipartimento di Scienze Cliniche Internistiche, Anestesiologiche e Cardiovascolari, Sapienza Università di Roma, Rome, Italy;* [g]*Center for Congenital Heart Diseases, Department of Pediatric Cardiology, Beatrix Children's Hospital, University of Groningen, University Medical Center, Groningen, the Netherlands;* [h]*Université Paris-Saclay, School of Medicine, Le Kremlin-Bicêtre, France;* [i]*Department of Cardiology, West China Hospital, Sichuan University, Chengdu, Sichuan, China;* [j]*Scottish Pulmonary Vascular Unit, Golden Jubilee National Hospital, Glasgow, United Kingdom;* [k]*Clinical Department of Respiratory Diseases, University Hospitals of Leuven and Laboratory of Respiratory Diseases and Thoracic Surgery (BREATHE), Department of Chronic Diseases and Metabolism (CHROMETA), KU Leuven –*

Abbreviations: 6MWD, Six-minute walk distance; 6MWT, Six-minute walk test; ACVRL1, Activin A receptor like type 1; BNP, Brain natriuretic peptide; BSA, Body surface area; CI, Cardiac index; CMR, Cardiac magnetic resonance; cMRI, Cardiac magnetic resonance imaging; CO, Cardiac output; CPET, Cardiopulmonary exercise testing; CTD, Connective tissue disease; DBH, Dopamine beta hydroxylase; DLCO, Diffusion capacity for carbon monoxide; ENG, Endoglin; ESV, End-systolic volume; FC, Functional class; HPAH, Heritable pulmonary arterial hypertension; HR, Hazard ratio; HR, Heart rate; IGFBP, Insulin-like growth factor binding protein; IPAH, Idiopathic pulmonary arterial hypertension; ISWT, Incremental shuttle walk test; LGE, Late gadolinium enhancement; LVEI, Left ventricle eccentricity index; mPAP, Mean pulmonary artery pressure; MRC, Medical Research Council; MS, Mass spectrometry; NIH, National Institute of Health; NT-proBNP, N-terminal pro-BNP; NYHA, New York Heart Association; PAPi, Pulmonary artery pulsatility index; PAWP, Pulmonary artery wedge pressure; PCa, Pulmonary arterial compliance; PH, Pulmonary hypertension; PHC, Pulmonary Hypertension Connection; PPHNet, Pediatric Pulmonary Hypertension Network; PVR, Pulmonary vascular resistance; RA, Right atrium/ right atrial; RAP, Right atrial pressure; RCT, Randomized controlled trial; REVEAL, Registry to Evaluate early and Long-term PAH Disease Management; RHC, Right heart catheterization; RHF, Right heart failure; RV, Right ventricle/Right ventricular; RVEDA, Right ventricular end-diastolic area; RVEF, Right ventricular ejection fraction; RVEI, Right ventricle eccentricity index; RVFAC, Right ventricular fractional area change; RVSD4, Standard deviation of the times to peak-systolic strain for the four mid-basal RV segments corrected to the R-R interval between two QRS complexes; SSc-PAH, Systemic sclerosis-associated PAH; ST2, Interleukin 1 receptor-like 1 protein; SV, Stroke volume; SVI, Stroke volume index; SvO2, Mixed venous oxygen saturation; TAPSE, Tricuspid annular plane systolic excursion; TTCW, Time to clinical worsening; WHO, World Health Organization; WSPH, World Symposium on Pulmonary Hypertension; WU, Wood units

Corresponding author: Raymond L. Benza MD, FACC, FAHA, FACP, FCCP Professor and Section Head, Cardiology Eastern Virginia Medical School, Macon and Joan Brock Virginia Health Sciences at Old Dominion University, George and Linda Kaufman Academic Chair of Cardiology, Sentara Health 825 Fairfax Ave, Suite 563 Norfolk, Virginia 23507

E-mail address: rxbenza@sentara.com.

[1] Drs. Sahay and Benza contributed equally to this manuscript.

https://doi.org/10.1016/j.healun.2025.04.015

University of Leuven, Leuven, Belgium; [l]Department of Pediatrics, Blalock-Taussig-Thomas Childrens Heart Center, John Hopkins University School of Medicine, Baltimore, MD; [m]Division of Pulmonary, Sleep and Critical Care Medicine, Tufts Medical Center, Boston, Massachusetts; [n]Normandie Univ, UNIROUEN, U1096, CHU Rouen, Department of Cardiology, Rouen, France; [o]George Washington University School of Medicine and Health Sciences, Washington, DC; [p]Division of Cardiovascular Medicine, Stanford Cardiovascular Institute, Stanford University, CA; [q]Division of Cardiovascular Medicine, Wexner Medical Center, College of Medicine. The Ohio State University, Columbus, OH; [r]Department of Respiratory Medicine and Infectious Diseases, Hannover Medical School, Hannover, Germany, and German Center of Lung Research (DZL), Hannover, Germany; [s]Cardiovascular Institute at Allegheny Health Network., Pittsburgh, PA; [t]Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of Rochester Medical Center, Rochester, New York; [u]Department of Medicine, Montefiore Medical Center, Bronx, NY; [v]Lahey Clinic, Boston; [w]Department of Clinical Sciences Lund, The Section for Cardiology, Lund University, and The Haemodynamic Lab, The Section for Heart Failure and Valvular Disease, VO. Heart and Lung Medicine, Skåne University Hospital, Lund, Sweden; [x]INSERM UMR_S 999, Hôpital Marie Lannelongue, Le Plessis-Robinson, France; [y]Cardiology Eastern Virginia Medical School, Macon and Joan Brock Virginia Health Sciences at Old Dominion University, George and Linda Kaufman Academic Chair of Cardiology, Sentara Health 825 Fairfax Ave, Suite 563 Norfolk, Virginia 23507; [z]Hôpital Erasme, University of Brussels, Belgium; [aa]Department of Medicine, Division of Pulmonary Medicine, University of Alberta, Edmonton, Canada; [ab]Department of Respiratory Medicine, Alfred Health, Melbourne, Australia; [ac]Advanced Lung Disease at AdventHealth Orlando, Orlando, FL; [ad]MD Heart Center, Children's Health, Division of Cardiology, Department of Pediatrics, UT Southwestern Medical Center, Dallas, TX.

1. EPIDEMIOLOGY, SURVIVAL AND OVERVIEW OF RISK STRATIFICATION

The 7th World Symposium for Pulmonary Hypertension (PH) defined PH as a resting mean pulmonary arterial pressure (mPAP) of > 20 mm Hg, as confirmed by right heart catheterization (RHC).[1] PH is divided into 5 clinical subgroups; pulmonary arterial hypertension (PAH), PH associated with left-sided heart disease, PH associated with chronic lung disease and/or hypoxia, PH associated with pulmonary artery obstructions, and PH with unclear or multifactorial etiologies.[1] Presently, an estimated 1% of the global population is affected by PH, including up to 10% of individuals older than 65 years[2]. The higher incidence among those > 65 years is attributed to the increased presence of cardiac and pulmonary etiologies of PH.[3–5] Regardless of etiology, PH is a complex pathophysiologic disorder that may involve multiple conditions and is frequently associated with deteriorating symptoms and increased mortality.

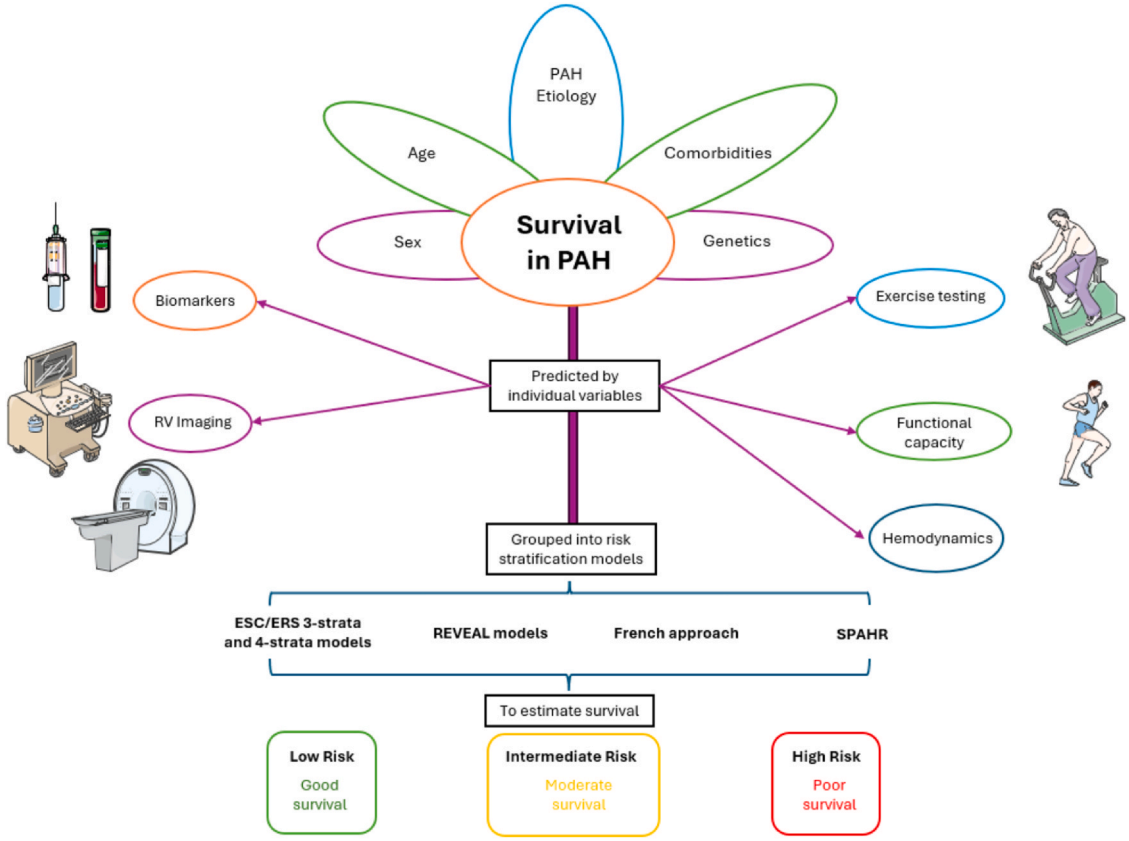
PAH remains a rare and incurable progressive disease, often leading to premature death[6]. Thus, it is essential to risk stratify patients with PAH to optimize their treatment and to identify those who are at a higher risk of clinical deterioration and/or death.

From a clinical perspective, the goal of PAH treatment is the achievement of low-risk stratum, which represents a favorable clinical response to treatment with an increase in short term survival.[7,8] Early initiation of interventions to enhance survival depends upon an accurate and prompt recognition of risk. Risk stratification tools provide guidance for clinicians on which clinical variables should be periodically and routinely monitored to inform care plans aimed at improving survival.[8] According to guidelines, these tools should be used at time of diagnosis and every 3–6 months thereafter. It is important to note that meaningful changes in risk scores can occur as early as 8–12 weeks after therapeutic changes[9] and knowing a patient's full risk spectrum is essential in clinical decision-making to target specific therapeutics, as well as for advanced care planning that includes activation of palliative measures, transplant, and other mechanical options (Figure 1). In this document we will review the key elements of these contemporary risk tools individually and within the context of these multivariable tools to provide the reader with enough practical knowledge to apply these systems in their daily practice.

Key points:

1. PAH is a rare, progressive disease that requires specialized care. This disease results in premature death, and risk stratification is essential to identify patients at a higher risk of clinical deterioration and death.
2. Risk assessment models aid clinicians to make decisions geared towards optimizing therapy and achieving a low-risk status. They should be used in conjunction with clinical gestalt.
3. Full spectrum of risk phenotyping is essential to inform treatment and advanced planning options.

Figure 1 Factors that influence survival in PAH and risk stratification models.



2. INDIVIDUAL RISK FACTORS AND RELATIONSHIP WITH MORTALITY AND MORBIDITY

Ongoing efforts to determine risk in patients with PAH utilize clinical data captured through large registries and clinical trial data. A deluge of studies since have identified multiple additional parameters associated with outcomes.[6] In clinical practice, each patient's prognosis and quality of life are of paramount importance. Multifactorial risk calculators, described later, help address these concerns by providing both baseline risk at the time of diagnosis, as well as re-assessment of risk at all follow-up visits.[8] Geographic registries including the PH Connection (PHC) registry,[10,11] the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL),[12–17] the French National Registry,[18–20] the Scottish Registry,[21] the European Comparative Prospective Registry of Newly Initiated Therapies for PH (COMPERA) registry,[22] the Swedish PAH Registry (SPAHR),[23–25] the U.S Food and Drug Administration (FDA) harmonized data collection,[26] as well as the large NIH sponsored US pulmonary vascular disease (PVD) OMICS cohort[27] and the ongoing pulmonary vascular research institute's (PVRI) Go Deep meta-registry[28] provide important information pertaining to risk and phenotype. The goal clinical outcome, irrespective of the calculator used, is for the individual patient to achieve the best possible survival, free of morbidity and with improved quality of life. This section provides an overview of individual risk factors predictive of outcomes in patients with PAH that were then assimilated into multimodality risk prediction tools.

2.1. Demographics

Key demographic risk factors for patients with PAH have been identified using registries, clinical trials, genetic and genomic studies, and investigations involving specific subsets of PAH (Table 1). This section summarizes the impact of these demographics on important outcomes.

Table 1 Demographic Risk Factors

Demographic	Risk	References
Older age	Worse outcomes	11,12,371
Female (except elderly)	More likely to develop PAH	6
Male	Increased mortality	11,33,372
Male >60 years of age	Increased 1-year mortality	12,15,117
BMPR2 mutation in females	Increased penetrance	21
PAH associated with systemic sclerosis	Higher 1- and 3-year mortality	32
PAH associated with portal hypertension	Presence of cirrhosis and increased severity are independent markers of higher mortality	373

2.2. Age and sex

PAH registries have been instrumental in expanding our understanding of the epidemiology and prognosis of PAH. Early registry data suggested that PAH predominantly affects young-to-middle age females, with a mean age of 36 ± 15 years and a female-to-male ratio of 1.7:1.[29] Contemporary studies now suggest that these early demographic characteristics are more reflective of heritable PAH (HPAH),[6] and that PAH is more frequently diagnosed in older individuals instead.[30] In addition, older age has been associated with worse outcomes.[12,21,31] Contemporary registries continue to identify female sex as a risk factor for the development of PAH in all but the elderly, with 62% to 80% of PAH cases reported in women[30]; elderly PAH patients appear to have a more balanced sex ratio. Paradoxically, male sex is independently associated with worse survival in PAH.[19,21,32,33]

Analyses involving the REVEAL registry have identified demographic variables (age and sex) as risk factors affecting survival.[12] In these analyses men >60 years of age were shown to have worse 1-year survival compared to women of similar age, with a greater than 2-fold increase in hazard ratio (HR).[12]. Therefore, this finding has been incorporated into the original REVEAL quantitative predictive algorithm and risk calculator,[33] as well as the revised REVEAL 2.0[34] risk calculator.

2.3. PAH etiology

2.3.1. PAH associated with systemic sclerosis

Patients with systemic sclerosis-associated PAH (SSc-PAH) have worse outcomes than patients with idiopathic PAH (IPAH) or other types of connective tissue disease (CTD)-associated PAH[35–40]. A meta-analysis involving 22 studies and 2244 patients with SSc-PAH showed pooled 1-, 2- and 3-year survival rates of 81%, 64% and 52%, respectively.[41,42]. Of note, prognostic factors typically observed in patients with IPAH (including age, male sex, diffusing capacity for carbon monoxide [DLCO], presence of a pericardial effusion, 6-minute walk distance [6MWD], mPAP, right atrial pressure [RAP] and cardiac index [CI]) were also prognostic factors in SSc-PAH.[41]

2.3.2. PAH associated with portal hypertension

One retrospective, longitudinal study involving 154 patients with porto-pulmonary hypertension (PoPH) identified the presence of cirrhosis (versus extrahepatic portal hypertension) and its severity (Child Pugh B and C) as independent markers of survival.[43] This finding was also noted in the REVEAL registry, where those with PoPH had almost a 2-fold higher risk of mortality. A retrospective review of PoPH patients included in the national registry of the United Kingdom National Pulmonary Hypertension Service showed a prevalence of 0.85 cases per million, balanced sex distribution, and a predominance of alcohol- and hepatitis C-related PoPH.[44] Survival was found to be poor, with rates of 85%, 60% and 35% at 1-, 3- and 5 -years, respectively. Of note, there were no differences in survival between patients with and without cirrhosis, and the severity of cirrhosis did not predict prognosis. Another study involving 154 patients with PoPH referred to the French National Center for PAH showed 1-, 3- and 5-year survival rates of 88%, 75% and 68%, respectively. Of note, this study observed worse survival in patients with cirrhosis compared to those without (p=0.003). In addition, the severity of cirrhosis was found to be a major

prognostic indicator.[43] An analysis of 174 patients with PoPH compared to 1478 patients with IPAH or HPAH in the REVEAL Registry showed a significantly worse 2-year survival from enrollment (67% vs 85%, $p < 0.001$), 5-year survival from time of diagnosis (40 vs 64%, $p < 0.001$) and 2-year freedom from all-cause hospitalization (49% vs 59%, $p < 0.019$) in the PoPH group compared to the IPAH/HPAH group.[45]

2.3.3. PAH associated with HIV infection

Outcome studies in patients with HIV-associated PAH (HIV-PAH) reflect the significant survival advantage resulting from treating both PAH and HIV. For example, a case control study involving 19 patients in the Swiss HIV Cohort Study showed a significant decrease in median survival in patients with HIV-PAH compared to HIV without PAH (1.3 vs 2.6 years, $p < 0.05$).[46] Of note, this study enrolled patients between 1988 and 1993, prior to specific treatments for PAH and the modern treatment era of HIV. A larger French study included 82 patients with HIV-PAH, 80% of whom were on simultaneous epoprostenol and combined anti-retroviral therapy.[47] Authors found the overall probability of survival at 1-, 2- and 3- years to be 73%, 60% and 47%. Importantly, the World Health Organization functional class (WHO-FC) was shown to predict survival, as patients with WHO-FC III-IV had lower 1-, 2- and 3-year survival rates (60%, 45%, and 28%) than patients with WHO-FC I-II (100%, 90% and 84%, respectively). Additionally, univariate analysis showed that a CD4 lymphocyte count greater than 212 cells/mm^3, combination antiretroviral therapy and epoprostenol infusion were related with better survival. On multivariate analysis, only a CD4 count > 212 cells/mm^3 remained independently associated with better survival (presumably due to the strong link between epoprostenol and combination antiretroviral therapy use in the patient population). Other studies have found that patients with HIV-PAH have a lower CD4 lymphocyte count and are more likely to have a detectable HIV viral load than patients with HIV and no PAH.[48] Observational studies have shown that in HIV-PAH patients, die more predominantly due to complications related to PAH.[47,49]

2.3.4. PAH associated with congenital heart disease (PAH-CHD)

PAH-CHD is a very heterogeneous group, and survival varies greatly depending upon the specific type of congenital heart disease (CHD). A retrospective study from the Netherlands, based upon two registries including children aged 0 to 17 years, showed better survival in children with PAH-CHD compared to children with IPAH at 1 year (77% vs. 62%), 2 years (70% vs. 50%) and 5 years (66% vs. 46%) after diagnosis.[50] There was one exception to this in children with an unrestrictive post-tricuspid shunt defect (eg, ventricular septal defects) who developed advanced PAH in the first weeks-to-months of life, as opposed to others with a pre-tricuspid shunt (eg, atrial septal defects) or an unrestricted post-tricuspid shunt who developed PAH in later childhood. Children with unrestrictive post-tricuspid shunt defect who rapidly developed advanced PAH early in life had a dismal survival, with none surviving at 1-year. In addition, children with PAH-CHD and concurrent genetic syndrome (i.e. Noonan's syndrome) were shown to be at increased risk for worse outcomes.

Adults with PAH-CHD are also at increased risk of death. A Dutch registry study involving over 11,400 patients with CHD aged 18 years or older showed a 3.1-fold increased risk of all-cause mortality for patients with PAH-CHD after adjusting for age, sex and CHD severity.[51] Among all the variables analyzed, PH had the highest hazard ratio for all-cause mortality. Several studies have investigated the prognosis of patients with Eisenmenger Syndrome (ES). Of the 353 patients with CHD in the REVEAL registry, 151 had ES. Their four-year survival following enrollment was 77%, similar to patients with IPAH, HPH and repaired CHD.[52] A multi-center study of 1098 patients with ES (age range 16.1 to 84.4 years) from Europe, Asia and the United States found that age (HR 1.41), pre-tricuspid shunt (HR 1.56), and presence of pericardial effusion (HR 2.41) were significant predictors of death, while resting oxygen saturation (HR 0.53), and presence of sinus rhythm (HR 0.53) were significant predictors of survival.[53]

It is worth noting that in PAH-CHD, the presence of an unrepaired shunt is associated with improved survival when compared to those with a repaired shunt. This has been demonstrated in several pediatric and adult cohorts.[54,55]

2.4. Functional capacity and exercise testing

2.4.1. Functional capacity

In patients with PAH, functional capacity is usually measured by the WHO modification of the New York Heart Association (NYHA) classification in patients with heart failure (Table 2).[56] The WHO-FC is one of the strongest

Table 2 World Health Organization Classification of Functional Status of Patients with Pulmonary Hypertension[56]

Class	Description*
WHO-FC I	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope
WHO-FC II	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
WHO-FC III	Patients with PH 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.
WHO-FC IV	Patients with PH with an inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity

PH = pulmonary hypertension; WHO-FC = World Health Organization functional class.

predictors of long-term survival, both at diagnosis and follow-up. This was initially demonstrated in two large cohorts of patients treated with intravenous epoprostenol[57,58] and has been further confirmed as an independent predictor of survival in subsequent registries.[12,19,24,32,59,60] In the REVEAL registry, patients with PAH who improved from WHO-FC III to I/II, whether newly or previously diagnosed and regardless of PAH cause, had better survival compared to patients who remained in WHO-FC III.[61] In a single center German cohort, changes in WHO-FC had a strong impact on survival and this was true for improvements as well as for deteriorations.[62]

2.5. Exercise testing

The six-minute walk test (6MWT) is the most widely used measure of exercise capacity in PAH and has been used as the primary endpoint in many pivotal drug trials.[63–67] Despite being dependent on age, sex, height, and weight, 6MWD is typically expressed in absolute distances rather than percentage of predicted. Investigators have not been able to agree on common predicted values in healthy adults, as large differences were often observed among studies.[68–70] While absolute values correlate with survival, changes in 6MWD were generally found not to be a good indicator of survival[71] or composite morbidity/mortality events. A large meta-analysis published in 2012, including 22 randomized trials and 3112 participants showed that improvements in 6MWD do not predict reduction of major clinical events in the short-term.[72] Subsequently, a detailed evaluation of the relevance of the 6MWD was conducted in the REVEAL Registry. Again, threshold values of < 165 or > 440 m defined the boundaries of high and low risk of clinical events, better than changes in distance walked.[12] Indeed, a sentinel article by Farber et al showed that a baseline 6MWD above vs below a threshold is a good predictor of one-year survival, while improvement in 6MWD is not. However, in this analysis, a decrement in 6MWD of > 15% was significantly associated with poorer survival (HR 1.20 [95% CI: 1.12–1.29]).[73]

A Medline search identified a total of 21 different threshold values for either single-point or change of 6MWD and these data were then analyzed in the COMPERA registry population. This analysis validated the prior thresholds of < 165 and > 440 m identified in REVEAL as the highest positive and negative likelihood ratios for all-cause mortality, respectively. In addition, the absolute single-point values outperformed changes in 6MWD for both improvement and worsening.[74] Refined threshold values from the REVEAL registry[34], < 165, 165–319, 320 to 440 and > 440 m, were adopted in both the COMPERA registry and French PH Registry risk stratification models,[75,76] and used in the most recent guidelines from the European Society of Cardiology (ESC) and European Respiratory Society (ERS) for the diagnosis and treatment of PH.[6] Regardless of its lack of association with survival, an increase in 6MWD of at least 33 m is associated with better quality of life and outcomes according to the SF-36 questionnaire.[77]

Measuring cardiac effort (CE) may offer a more stable and treatment-sensitive value as compared to raw 6MWD.[78–80] CE requires a continuous, electrocardiographic measure of heart rate. CE is calculated as ([# of heart beats during 6MWT]/6MWD). By incorporating changes in heart rate, CE stabilizes the raw 6MWD measure against day-day changes in effort, mood, or musculoskeletal pain, and therefore makes treatment-attributable improvements and clinical worsening easier to measure. This day-day variability in 6MWD, especially at longer walk distances,[68,79] is probably the cause of the described 'ceiling effect' for 6MWD. CE gives insight into stroke volume, potentially recognizing patients with more severe stroke volume impairment.[78,80]

The incremental shuttle walk test (ISWT) is an externally paced incremental walking test that can be used as an alternative to a maximal exercise test for assessing patients with PAH.[81] Despite potential advantages to the 6MWT like not having a ceiling effect on distances, the ISWT is not commonly used in patients with PAH.

Cardiopulmonary exercise testing (CPET) is a more comprehensive way to evaluate exercise capacity in patients with PAH as it helps identify factors at the ventilatory, cardio-circulatory, and/or muscle/metabolic level that may contribute to reduced functional capacity and exercise intolerance.[82] Characteristics of PH are reduced peak oxygen consumption (peak VO2) together with strongly increased ventilatory volume/carbon dioxide output (VE/VCO2) slope.[83] Peak VO2 is a common readout from CPET and is a prognostic marker in patients with heart failure.[84]. Both parameters have been associated with survival in patients with PAH.[85–89]

Studies utilizing CPET for PAH have found low peak VO2 to be predictive of survival with variable cut-off points of 10.4,[90] 11.5,[87] and 13.2 mL/min/kg.[91] Cut-off points for peak VO2 by consensus include < 10 mL/min/kg as poor prognosis and a need to escalate therapy and > 15 mL/min/kg indicating a better prognosis.[92] Also, a high VE/VCO2 slope can indicate pulmonary gas exchange limitations.[82] The development of a right to left shunt on exercise testing (excluding CHD PH patients) is associated with worse survival and can be highlighted by CPET.[93]

Recently, CPET proved useful as a prognostic measure over time in patients with repaired and unrepaired atrial septal defects.[94] CPETs are not broadly performed given their complexity and despite initial studies, CPET only marginally adds to risk prediction compared with 6MWT in PH.[91,95] However, it is still recommended as a measure to determine severity of exercise impairment and prognosis.[96] CPET may also have a role in evaluating symptomatic patients at high risk for developing PAH (i.e. connective tissue disease)[97] and is currently being evaluated in early PAH drug development studies.

Lastly, exercise treadmill testing (ETT) may be an alternative to 6MWT and CPET.[98] The Naughton-Balke ETT protocol is a total of 20 min or 11 metabolic equivalents (METs) and has several advantages. Since its inception, the Naughton-Balke ETT protocol has served as a reliable, objective, non-invasive test which has been validated in the cardiac catheterization laboratory as a predictor of oxygen consumption during exercise. Treadmill testing is more standardized than the 6MWT, is an objective non-timed test, and less expensive and more widely available than CPET. Using the Naughton-Balke exercise protocol,[99] a modified functional assessment exercise test using metabolic equivalents (METs) was a reliable measure of exercise capacity in PAH and correlated with 6MWD. Using generalized logistic regression models, ETT had similar reliability and reproducibility, and discriminative ability between good and poor functional class (FCI-II vs III-IV) as the 6MWT.[98] In addition, METs appeared to be more sensitive than 6MWD in detecting changes in exercise capacity in less sick patients.

In a follow-up study, reduced exercise capacity on ETT was associated with abnormal hemodynamics and was a predictor of death.[100] Reduced exercise capacity was an independent predictor of death in the more homogenous subgroup of patients with PAH and in the entire cohort of PH patients, including FC I-II patients. The association persisted even excluding patients on treatment for PAH.[100] In addition it was well-tolerated with no adverse events even in the FC IV patients similar to the original findings by Patterson.[99] Finally, to complete its prognostic significance, investigators evaluated ETT in the REVEAL risk score.[101] In patients who lacked 6MWT data, ETT of < 1.5METs, 1.5–5 METs and ≥ 5 METs strata performed well in the equation and improved estimates of predicted versus observed survival.[101] The REVEAL equation with ETT improved prediction accuracy most in the high-risk group.

2.5.1. Actigraphy, remote sensing and wearables

Recently, wearable devices are being investigated to passively measure free living physical activity and quantify benefit from PAH drugs.[102,103] Daily physical activity in patients receiving selexipag or placebo was measured in the TRACE trial but no treatment-attributable differences in daily step counts or activity time were found.[102] Another study paired a text-based mobile health intervention with actigraphy and demonstrated that the intervention group had a significantly greater average number of steps at week 12 after adjusting for baseline step count, age, sex, WHO-FC, and enrollment quarter.[104] These studies highlight the remarkable degree of inactivity in patients with PAH and the impact that intrinsic behavior has on activity; even with measurable clinical improvement, total daily activity may not change (because it reflects behavior more than capacity for activity).

Peak steps, a novel way to evaluate capacity for activity which counts steps only during the most active minutes, increased in prospective cohorts after adding PAH therapies and after a behavioral intervention, even though total daily activity did not change.[103] It's noteworthy that peak steps were unchanged in stable PAH

patients and correlated well with Emphasis-10 scores, suggesting that this is an objective activity measure that relates to quality of life.

Wearable devices also offer the option of an active, unsupervised, home 6MWT.[80] By incorporating heart rate monitoring and calculating CE, a comparable measurement can be obtained in the clinic and home setting. It is too early to include actigraphy or home 6MWD/CE in current risk assessments because more work is necessary to establish minimal clinically important differences. However, peak steps and cardiac effort may be sensitive to interventions in patients with PAH allowing clinicians to test treatment responses passively using actigraphy.

2.6. Circulating biomarkers and laboratories

The use of circulating biomarkers offers several advantages in the risk stratification of patients with PAH, including an objective and rapid measurement, that is easy and safe to perform (i.e. venipuncture), while less expensive than imaging or echocardiographic studies, and convenient for frequent testing during follow-up.[8] For these reasons, many investigations have tested biochemical markers to assess prognosis in PAH.[105,106] Biomarkers tested in PAH can be grouped according to their involvement in certain critical pathophysiological mechanisms (Table 3).[7] Although results with some of them are promising, they have not yet been incorporated in clinical practice due to the lack of external validation in larger cohorts and multivariable adjustment for traditional measurements of risk in PAH.[6,34]

Brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are the only prognostic biomarkers that are clinically available at this point. BNP and NT-proBNP are synthesized predominantly by ventricular cardiomyocytes in response to ventricular stretch.[107] The increased ventricular wall stress results in the synthesis of pre-proBNP, which undergoes two cleavages to form biologically active BNP and the inactive amino terminal fragment NT-proBNP. NT-proBNP has a longer half-life (70 min) compared with BNP (22 min), resulting in better stability during storage and higher levels in the blood.[107–109]

In PAH, higher levels of BNP and NT-proBNP are associated with worse functional capacity, right ventricular (RV) function, and survival.[12,110–113] In fact, in the REVEAL registry, PAH patients with BNP of > 340 pg/mL had a 3.6-fold increase in 5-year mortality when compared with patients with BNP levels ≤ 340 pg/mL.[110] Survival estimates at 5-years were 72.9% versus 32.5% for patients with BNP below or above this cut-off. A recent meta-analysis in PAH patients showed that higher baseline NT-proBNP levels were associated with a greater risk of mortality or lung transplant, with an adjusted HR of 2.5 (when reported as dichotomous cut-off value) or 1.19 (when calculated as a two-fold difference of the weighted mean in continuous scales).[114]

A BNP reduction during follow-up was associated with better survival, whereas an increase in BNP was associated with higher mortality in patients with PAH.[110] Similarly, increasing levels of NT-proBNP over time was also associated with higher mortality,[62,115] and a decrease of 15% in a year correlated with better survival.[115]

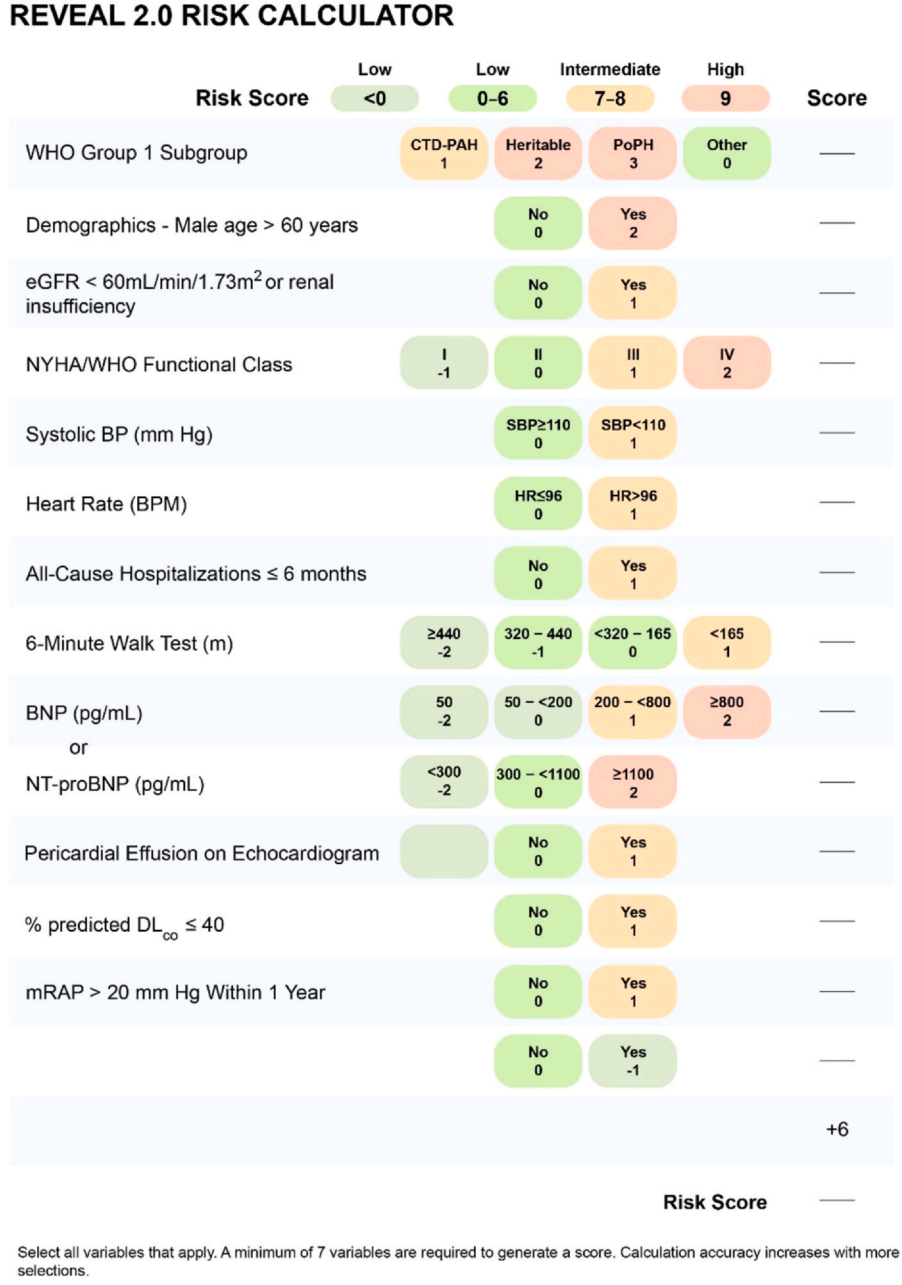
Table 3 Promising Circulating Biomarkers to Assess Risk in PAH

Vascular Cellular Dysfunction	Inflammation	Vascular Remodeling	Metabolic Alteration	Myocardial Stress	Low Cardiac Output / Tissue Hypoxia and/or Damage	Iron Status	Coagulation
-Asymmetric dimethylarginine -Endothelin–1 -Angiopoietins -Micro RNA -von Willebrand factor	-C-reactive protein, -Interleukin 6 -Complement factor H and D -C-X-C motif chemokine ligand -β-NGF -TRAIL -Actin A -FSTL3	-Bone morphogenetic proteins 9 and 10 -Tissue inhibitors of metallo proteinase -Apolipoprotein-E -Insulin growth factor -Translationally controlled tumor protein	-Adiponectin -Low density lipid-cholesterol -High density lipid-cholesterol	-BNP/NT-proBNP -Soluble ST2 -Troponins	-Growth differentiation factor 15 -Osteopontin -pCO_2-uric acid -lactic acid -mixed venous O2 -Sodium and chloride	-Iron studies, -Erythropoietin -Red blood cell distribution width	-Plasminogen

Furthermore, the increase in NT-proBNP during follow-up (3–12 months) remained independently associated with mortality in a multivariate model.[62] NT-proBNP was measured at regular intervals in the controlled clinical trial GRIPHON that randomized patients with PAH to selexipag or placebo.[116] Authors tested NT-proBNP thresholds based on tertiles < 271 pg/mL, 271 to 1165 pg/mL, > 1165 pg/mL or the 2015 ESC/ERS guidelines cutoffs: < 300 pg/mL, 300 to 1400 pg/mL and > 1400 pg/mL.[7116] These NT-proBNP thresholds, both at baseline and follow-up, provided valuable prognostic information and predicted treatment response.[116]

In the REVEAL 2.0 risk calculator (Figure 2), the BNP or NT-proBNP cut-off values were expanded when compared to the original version of the calculator. The REVEAL Lite 2 risk calculator uses the same cut-off values for

Figure 2 REVEAL 2.0 risk score calculator.[62].



BNP and NT-proBNP as the full version of the calculator.[117] The 2022 ESC/ERS guidelines recommend to assess PAH severity using a panel of data that take into account BNP and NT-proBNP (recommendation Class IB), both for the three-stratum risk stratification model at time of diagnosis or the four-stratum risk stratification model during follow-up, borrowing the cut points from the original REVEAL 2.0 and spitting the intermediate range into "intermediate low" and "intermediate high" ranges.[6,16] Tables 4 and 5 highlight the cut offs of BNP and NT-proBNP as it has been recommended by REVEAL, ESC/ERS guidelines and the four strata scheme by COMPERA 2.0.[6,75]

It is important to recognize certain limitations when interpreting the levels of BNP and NT-proBNP since they can be elevated in other conditions including left heart disease and impaired renal function.[118,119] Female sex and older age are associated with higher levels,[120,121] whereas obesity is associated with lower circulating levels of BNP and NT-proBNP.[122,123] Other factors that may affect the plasma levels include intra-individual biological variation,[124] time of sample, prior physical exertion, and the immunoassay used.[109] No data are available comparing BNP versus NT pro-BNP regarding prognostication; furthermore, there is no universal conversion factor between the two determinations.

Although NT-pro/BNP is an excellent protein biomarker of right heart failure (RHF), proteomic discovery methods have identified new circulating proteins associated with PH severity. Proteins are dynamic and can be better indicators of severity and response to therapy than non-protein markers, like imaging and demographics. Biomarkers like insulin-like growth factor binding protein 4 (IGFBP4),[125] endostatin, and soluble interleukin 1 receptor like 1 (ST2)[126] have enhanced the prediction quality of our contemporary systems and should be considered as adjunctive measures to ensure the most comprehensive discrimination possible.

At present, the challenge is to identify novel biomarkers that provide incremental information to current risk stratification models. A recent study additionally identified three biomarkers independently associated with survival in two different PAH cohorts.[127] β-nerve growth factor (β-NGF) and CXC motif chemokine ligand 9 (CXCL9) were predictors of death or lung transplantation, whereas high levels of TNF-related apoptosis-inducing ligand (TRAIL) were associated with better prognosis.[127] The prognostic value of these biomarkers was more powerful than the non-invasive variables WHO-FC, 6MWD, and BNP/NT-proBNP.[127] Moreover, Activin-A and FSTL3 has been identified as prognostic in PAH, independent of risk stratification.[128]There is also an attempt to

Table 4 Risk Stratification Table from the 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension[7]

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5-10%)	High risk (>10%)
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165-440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 mL/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11-15 mL/min/kg (35-65% pred.) VE/VCO_2 slope 36-44.9	Peak VO_2 <11 mL/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50ng/L NT-proBNP <300 ng/L	BNP 50-300 ng/L NT-proBNP 300-1400 ng/L	BNP >300 ng/L NT-proBNP >1400 ng/L
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18-26 cm^2 No or minimal pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m^2 SvO_2 >65%	RAP 8-14 mmHg CI 2.0-2.4 L/min/m^2 SvO_2 60-65%	RAP >14 mmHg CI <2.0 L/min/m^2 SvO_2 <60%

Abbreviations: 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; CMR, cardiac magnetic resonance; NT-proBNP, N-terminal pro-brain natriuretic peptide; pred., predicted; RA, right atrium; RAP, right atrial pressure; SvO2, mixed venous oxygen saturation; VE/VCO2, ventilatory equivalents for carbon dioxide; VO2, oxygen consumption; WHO, World Health Organization

[a]Most of the proposed variables and cut-off values are based on expert opinion.

[b]Occasional syncope during heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.

Table 5 Risk Stratification Table From the 2022 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension[6]

Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5-20%)	High risk (>20%)
Clinical observations and modifiable variables			
Signs of right HF	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope[a]	Repeated syncope[b]
WHO-FC	I, II	III	IV
6MWD[c]	>440 m	165-440 m	<165 m
CPET	Peak VO_2 >15 mL/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11-15 mL/min/kg (35-65% pred.) VE/VCO_2 slope 36-44	Peak VO_2 <11 mL/min/kg (<35% pred.) VE/VCO_2 slope >44
Biomarkers: BNP or NT-proBNP	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50-800 ng/L NT-proBNP 300-1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
Echocardiography	RA area <18 cm^2 TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion	RA area 18-26 cm^2 TAPSE/sPAP 0.19-0.32 mm/mmHg Minimal pericardial effusion	RA area >26 cm^2 TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion
cMRI	RVEF >54% SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37-54% SVI 26-40 mL/m^2 RVESVI 42-54 mL/m^2	RVEF <37% SVI <26 mL/m^2 RVESVI >54 mL/m^2
Hemodynamics	RAP <8 mmHg CI ≥2.5 $L/min/m^2$ SVI >38 mL/m^2 SvO_2 >65%	RAP 8-14 mmHg CI 2.0-2.4 $L/min/m^2$ SVI 31-38 mL/m^2 SvO_2 60-65%	RAP >14 mmHg CI <2.0 $L/min/m^2$ SVI <31 mL/m^2 SvO_2 <60%

Abbreviations: 6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; cMRI, cardiac magnetic resonance; CPET, cardiopulmonary exercise testing; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; pred., predicted; RA, right atrium; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; SvO2, mixed venous oxygen saturation; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; VE/VCO2, ventilatory equivalents for carbon dioxide; VO2, oxygen consumption; WHO-FC, World Health Organization functional class.

[a]Occasional syncope during heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.

[b]Repeated episodes of syncope, even with little or regular physical activity.

[c]Observe that 6MWD is dependent upon age, height, and burden of comorbidities.

find indicators of PH severity that are more specific to the lung vasculature, which can overcome the known clinical hurdles of natriuretic peptides. In addition, the complex processing of messenger ribonucleic acid (mRNA) and alternate splicing may make mRNA a better choice than simple proteins as a PH biomarker.

The discovery methods for novel protein biomarkers are either "non-biased" with the discovery approach open ended such as mass spectrometry (MS) or "validated" where specific proteins are assayed, such as multiplex ELISAs or aptamer-based assays. Both approaches can be very powerful. MS-based approaches, especially for serum/plasma, are labor intensive and require substantial sample pre-processing. The yield is generally 800–1000 proteins and has the advantage of identifying potential protein modifications such as phosphorylation that could inform PH pathobiology. Targeted approaches require less pre-processing and are faster. The yield is based on the analytic platform used with multiplex ELISA assays good for ~300 proteins, to the unique aptamer assays (Somascan, Boulder, CO) in which thousands of proteins are quantified. MS and aptamer analytic methods are both semi-quantitative and need to be verified with an alternative method such as ELISA and preferably with a new cohort. Presently aptamer-based targeted discovery has the greatest depth of protein identification.

PH proteomics was recently reviewed in detail.[129] MS identified potential circulating PH severity biomarkers including leucine-rich α2 glycoprotein (LRG),[130] ADIPO, alanyl aminopeptidase (ANPEP), dopamine beta hydroxylase (DBH), glycoprotein Ib platelet subunit alpha (GP1BA), G protein alpha S (GNAS), and telomeric repeat-binding factor 1 (TRF1),[131] and insulin-like growth factor binding proteins (IGFBPs).[132] The MS approach

was also used to successfully identify proteins associated with metabolic pathway proteins in PAH.[133] The aptamer-based approach using Somascan has been used in serum and plasma to identify proteins distinct to SSc-PAH,[134] and PAH survivors vs non-survivors and severity.[135,136] Targeted ELISA has shown significant severity associations with Elastase/Elafin,[137] and inflammatory proteins.[138] The issue of circulating biomarkers specifically in PAH was furthermore recently addressed in a recent state of the art review, reflecting on future directions.[139]

Lung tissue has also been used to directly identify lung-specific PH related proteins.[42,140] Using a carefully assembled RV failure discovery and validation cohort, a multiplex ELISA was used to identify a plasma protein phenotype of RV failure.[141] Although the significance of these discoveries can't be underestimated, many fall short in not comparing their performance to the current clinical benchmark BNP. Unfortunately, none of the discovered blood biomarkers have crossed the discovery chasm into the clinic. Ultimately, a logical fit would be demonstration of improved risk stratification with the inclusion of additional biomarkers into the current clinical risk calculators such as REVEAL or the ESC/ERS tools as has been shown for soluble interleukin 1 receptor-like 1 protein (ST2), interleukin 6 (IL6) and endostatin.[126,142–145]

In the REVEAL registry, renal insufficiency was strongly associated with worse survival and this was subsequently confirmed in the updated REVEAL calculator[12,146]; a ≥10% decline in eGFR from baseline over a year was associated with increased in risk of death.[147] Elevated cardiac troponin is associated with right ventricular dysfunction and worse outcomes in PAH patients.[148,149] Hyponatremia predicts worse outcomes in PH patients even after adjusting for other parameters including right atrial pressure, cardiac index and diuretic use.[150] Serum chloride at 6 months from the PAH diagnosis was a strong and independent predictor of mortality in patients with IPAH/HPAH, even after adjusting by serum sodium, renal function, diuretic, and prostacyclin analog use.[151] Lower serum albumin and sodium levels are associated with mortality, as are total bilirubin, creatinine, BUN, and uric acid.[152] Uric acid is also predictive of time to clinical worsening (TTCW) and 6MWD. Coupled with these associations is the finding that uric acid levels are reduced by PAH therapies.[153] Markers of inflammation like C-reactive protein (CRP), thrombosis and platelet activation and interleukins are also associated with worse outcomes in PAH.[154,155] Lastly, markers of impaired glucose metabolism and increased insulin resistance, as well as thrombocytopenia, also associate with adverse outcomes.[156,157]

Key points:

1. Reanalysis of registry data, as well as prospective data collection using active registries, clinical trials, and other real-world data are needed to update our understanding of how demographics influence outcomes.
2. Immutable risk factors like age, sex and subset of PAH can add predictive value to modifiable factors
3. Functional capacity whether subjective (WHO-FC) or objective (6MWT, ISWT, ETT, CPET) retains vital predictive value. We suggest the 6MWT for routine assessment of PAH patients due to its being cheaper, ease of operability and reproducibility.
4. Remote monitoring and sensors for objective measures of exercise capacity are promising but need further standardization and validation.
5. Basic laboratory measures remain essential parts of risk prediction, particularly those that represent vital organ function
6. Although several circulating biomarkers are promising, only BNP and NT-proBNP are broadly used clinically for prognostication both at baseline and follow-up.
7. Higher blood levels of BNP and NT-proBNP are associated with worse functional capacity, right ventricular (RV) function and survival. Increasing levels of these biomarkers over time are associated with higher mortality, while decreasing levels are related with better survival.
8. Proteomic discovery using MS or other techniques holds promise of identifying new biomarkers that can be added to contemporary risk scores to improve mortality and morbidity risk predictions.

2.7. Imaging modalities

RHF is the clinical cornerstone underlying disease progression in patients with PAH. Although some risk assessment models rely on clinical evaluation and biomarkers, imaging of right ventricle provides significant prognostic information and it avoids the need for repeating invasive testing, like RHC. Furthermore, imaging is typically a low-cost and easily accessible modality, particularly echocardiography, making it attractive for serial

risk assessment,[158] monitoring disease progression or therapeutic responses. Imaging to evaluate disease severity in PAH is a 1B recommendation from the 2022 ESC/ERS PH guidelines.[6,8] The European guidelines state, "*The rationale for the reported imaging measurements is strong, as RV systolic function metrics assess the adaptation of RV contractility to increased afterload, and increased right heart dimension and inferior vena cava dilation reflect failure of this mechanism, hence maladaptation… All these variables are physiologically interdependent, and their combination provides additional prognostic information over single measurements".* Hence the importance of adjuvant imaging in PAH risk assessment cannot be understated.

2.7.1. Echocardiography

Several echo-indexes are currently used in daily practice to predict risk in PAH, but they were mostly validated in single center studies, with limited patient cohorts. The most commonly used and best validated parameters are included in the ESC/ERS guidelines, and include[6]: right ventricular fractional area change (RVFAC),[159] tricuspid annular plane systolic excursion/systolic pulmonary artery pressure (TAPSE/sPAP),[160,161] RV isovolumic peak velocity by tissue doppler imaging (TDI),[162] and RV dyssynchrony by 2D strain.[163,164] Transthoracic echocardiogram findings of advanced PAH associated with adverse outcome include RVFAC < 36.5%, TAPSE/sPAP < 0.34mm/mmHg, RV isovolumic peak velocity ≤ 9 cm/s, and RVSD4 (standard deviation of the times to peak-systolic strain for the four mid-basal RV segments corrected to the R-R interval between two QRS complexes) > 23 ms.Echocardiography has its own limitations with reproducibility and interobserver variability. Body habitus of the patient and operator experience may also play a role in the interpretation of the findings. Despite its advantages, larger multicenter studies are lacking because most of the real-world registries did not prospectively collect echocardiographic data due to cost.

Serial imaging data on a patient may guide clinical judgment or treatment decisions. Specifically, it has been shown that improvement in RV end-diastolic area (RVEDA) (Δ −2.45 cm2), right atrial (RA) area (Δ −1.3 cm2) and LV-eccentricity index (LVEI) (Δ −0.12), (i.e. signs of right heart reverse remodeling), can be targeted to improve patient's prognosis or escalate therapy.[165,166] The incorporation of echocardiography in the risk stratification is limited somewhat by the lack of large prospective observational studies or multicenter registries validating these parameters and should be an area of future investigations. However, several large ongoing echocardiographic registries in Italy and Australia, as well as the incorporation of imaging in many prospective phase 2 and 3 studies of new therapeutics in PAH may shed significant new data on the applicability of echocardiography for primary risk prediction tools.

2.7.2. Cardiac MRI

Cardiac magnetic resonance (CMR) imaging is the gold-standard method for ventricular quantification, especially for the RV since 3D RV echocardiography usually underestimates volumes compares to CMR.[167] Inter- and intra-observer variability with CMR has remained a challenge, although to less extent than echocardiography. In addition, CMR incorporates a variety of techniques, beside cine imaging, to assess structure and function like flow quantification for tricuspid regurgitation,[168] first-pass perfusion sequences for quantitative myocardial perfusion[169] and pulmonary transit time,[170] T1 mapping and extracellular volume (ECV) mapping for assessment of diffuse fibrosis,[171] and late gadolinium enhancement (LGE) imaging for focal fibrosis.[172,173] Lastly, with CMR, it is possible to measure estimated RV to pulmonary arterial coupling, a parameter that is approximated by echocardiography using TAPSE/sPAP (see below for detailed description).[174,175]

RV ejection fraction (RVEF) has become an important prognostic marker and a baseline RVEF < 35% predicts 1-year mortality in PAH and decline in RV systolic function independently of classical hemodynamic predictors of outcome.[176] A larger follow up study demonstrated that although both invasive hemodynamics and CMR have similar prognostic value at follow-up, only improvement in RVEF by CMR predicted PAH survival at 5 years.[177] A meta-analysis of over 500 PAH patients in eight different studies investigating 21 different CMR findings demonstrated that a 5% decrease in RVEF was the strongest predictor of mortality with pooled HR of 1.23 per every 5% reduction in RVEF.[178] Another meta-analysis including 1120 patients, demonstrated that RVEF was the only parameter that predicted all-cause death and composite endpoints.[179] A recent meta-analysis including 1938 patients showed a 4.9% increase in clinical worsening and 2.1% increase in the risk of death per single percent decrease in RVEF.[180]

In addition to RVEF the RV stroke volume (SV), relative change in area of the pulmonary artery (PA) and RV end-systolic (ESV) and end-diastolic (EDV) volumes indexed to body surface area (BSA) have also emerged as a

clinically relevant treatment targets[181–184] using cMRI·Specifically, the RV ESV index predicted outcomes and improved risk stratification when used in conjunction with the REVEAL 2·0 risk score calculator·[185] RV eccentricity index (RVEI) defined by the ratio of the RV length over RV width as measured in the mid ventricular short axis slice is also an independent predictor of adverse outcome·[186] In the most recent ESC/ESR 2022 PH guidelines, RVEF, indexed RVSV, and indexed RVESV are included as CMR risk variables, with cutoff values provided to identify patients at low (< 5%), intermediate (5–20%), and high (> 20%) risk of death within 1 year of diagnosis.[6]

Several additional CMR parameters have been explored in PAH. LGE is commonly seen in RV insertion sites and is a predictor for adverse outcomes, albeit not superior to RVEF.[173,187] Native T1 mapping and ECV have been shown to be elevated in PAH at the RV insertion points and are associated with decreased RV function and increased RV size.[171] In a small study of 30 patients, T1 values of the RV free wall were independently associated with composite events of death or hospitalization.[188] Using machine learning, 3D RV motion derived from CMR cine imaging of RV was able to discriminate survival more than RVEF, and performed even better than other CMR volumetric parameters, hemodynamic parameters, and 6MWD.[189] Studies using newer CMR techniques such as 4D flow have shown that lower RV flow provided incremental value over RVEF alone for predicting impaired exercise capacity and could reliably identify PAH patients with intermediate and high-risk profiles.[190] Lastly, RA longitudinal strain imaging was shown to aid in differentiating compensated PAH versus decompensated PAH patients, the latter at higher risk of clinical worsening.[191]

Beyond identifying specific imaging parameters useful for risk stratifying PAH patients, CMR has provided important insights into disease pathophysiology and phenotyping. In one study from the ASPIRE registry focusing on age- and sex-matched controls, male IPAH patients tended to have lower RVEF and SV compared to females, despite similar RV afterload.[192] These findings are consistent with converging lines of evidence suggesting that estradiol levels associate positively with RVEF and inversely with RV ESV by CMR,[193] providing a possible pathophysiological correlate for understanding the 'sex paradox' of pulmonary vascular disease in which higher prevalence but more favorable outcome are observed in women compared to men.[194] Furthermore, measurement of RV mass/volume ratio enabled the identification of a more adaptive RV phenotype to increased afterload.[195] Indeed, a RV mass/volume value > 0.45 was able to identify those patients with a more favorable right heart remodeling pattern associated with improved outcome[196] and serial measures of RV mass revealed adaptative RV hypertrophy in survivors with PAH.[197–199]

In summary, CMR has emerged as a non-invasive method of choice when available to assess right heart remodeling, prognosis, and treatment effects in PAH patients. RVEF is a robust imaging parameter that has been shown by multiple studies to be prognostic. Additional CMR parameters may further refine prognosis. CMR will likely play a greater role in the management of PAH in the future. However, this may be hindered by its cost and availability.

2.7.3. Imaging assessments of RV/PA coupling

One key contemporary advance in pulmonary vascular disease gleaned from imaging is the assessment of RV/PA coupling, or the efficiency of RV work relative to pulmonary circulatory flow.[200]. This parameter is measured directly using the ratio of arterial to ventricular elastance (Ees/Ea) via serial assessments of pressure volume loops during cardiac catheterization and is considered a key parameter in predicting RV failure in PAH. Both echocardiography and cMRI can give approximations of this value. Using echocardiography, the parameter of TAPSE/sPAP is conventionally thought of as a surrogate of coupling. In twenty-eight stable PAH patients, a TAPSE/sPAP lower than 0.25 mm/mmHg was found to have a worse prognosis compared with those patients with a higher value.[201] A TAPSE/sPAP ratio ≤ 0.32 mm/mmHg is a predictive risk marker for all-cause mortality in scleroderma patients with PAH.[202] In addition, in medically treated CTEPH patients, a TAPSE/sPAP ratio ≤0.20 had lower survival rates and TAPSE/sPAP ratio≤0.20 combined with NYHA-FC III-IV was an independent predictor of poor prognosis.[203]

Coupling can also be extrapolated more accurately by the ratio of RV SV/ESV measured either by CMR or multi-slice computed tomography. When RV cavitary volume is assessed by CMR within 24 h of RHC, RV/PA coupling (quantified by the Ees/Ea ratio) decreases with increasing RVEDV and pulmonary arterial stiffness. In PH patients, Ees/Ea < 0.805 was able to predict future RV failure.[204] Using this approach, RV/PA coupling as estimated by RV SV/ESV has been found to independently predict transplantation-free survival after adjusting for cardiopulmonary hemodynamic variables in different PH cohorts with values of < 0.515–0.534 predictive of survival,[205,206] including pediatrics using 3D echocardiography.[207] RV/PA coupling has also been assessed using

TAPSE or RV global longitudinal strain (GLS) obtained from speckle tracking analysis and sPAP from hemodynamic assessment. RVGLS/sPAP was better at predicting clinical endpoints than RVGLS/pulmonary vascular resistance (PVR) and RVGLS*PA compliance.[208]

Thus in lieu of more invasive and less readily available pressure volume loop assessments, cardiac imaging using echocardiography or MRI can offer a fast, semi-reliable and easy to obtain estimates of this important predictive parameter and can be used serially to evaluate RV adaptive or maladaptive remodeling.

2.7.4. Positron emission tomography (PET)

PAH causes chronic inflammation with or without significant atherosclerosis in the pulmonary arterial wall, leading to accumulation of metabolically active and proliferative inflammatory cells.[209] These immune cells have high metabolic activity demonstrated by avidity for 18F-FDG, which can be detected by PET.[210] Increased FDG uptake in the RV has been shown to correlate with severity of PAH and standard prognostic biomarkers such RV size and function, 6MWD and BNP/NT-proBNP.[201,211] Similarly, in a cohort of patients with PH associated with sarcoidosis, uptake of FDG in the main pulmonary artery was found to have a specificity of 100% for the detection of PAH and to correlate with markers of disease severity.[212]

Future studies will be required to better understand the additive role of this novel imaging in combination with routine and/or boutique PET tracers[213,214] in the risk stratification of patients with PAH across various WHO etiology, and for monitoring response to therapy.

Key points:

1. Echocardiography is a low-cost, non-invasive, readily accessible modality that provides diagnostic and prognostic information and may be used to complement the risk stratification score by any method.
2. Cardiac MRI provides detailed information about right ventricular function and may provide additional information above echocardiography, but its incorporation in the routine clinical practice is limited due to cost, availability, and complexity. Larger clinical studies are needed to highlight its role in routine clinical practice.
3. There is a need for future, multicenter, rigorous studies looking at systematic integration of imaging with clinical assessment, risk scores and biomarkers.

2.8. Hemodynamics parameters

Numerous studies have evaluated the prognostic utility of hemodynamic variables at the time of PAH diagnosis, as well as change of hemodynamic parameters after treatment appear to have an even greater prognostic significance.[62,215–217] Importantly, RHC-based hemodynamics have not been traditionally included in phase 3 PAH clinical trials as primary endpoints.[218] National and international PAH registries, from which the conventional risk-stratification scores have largely been derived, may or may not measure all the hemodynamic variables in their reporting, especially during follow-up, limiting their availability and 'weighting' in such scores. Hemodynamic variables are included in the 2022 ESC/ERS guidelines risk stratification approach (Table 5), but in clinical practice risk assessment can be performed without needing these additional hemodynamic data.

Historically, mPAP was a prognostic factor,[58] but has not been associated with outcomes in more contemporary cohorts. This is because the degree of elevation in pulmonary arterial pressure does not account for whether RV dysfunction is present, though achieving a mPAP < 35 mmHg may be associated with better survival.[219] Hemodynamic variables that reflect RV function such as CO, cardiac index (CI), and stroke volume index (SVI) have been consistently linked to outcomes. CO, CI and RAP have been associated with survival in PAH at the time of diagnosis.[6,20,220] Achieving a CI ≥2.5 L/min/m^2 portends a lower risk of morbidity or mortality and is the treatment target endorsed in European guidelines.[7,62,217] Mixed venous oxygen saturation (SvO_2), an indicator of CO and peripheral oxygen extraction is also associated with survival in PAH and may be superior to CI in its prognostic utility.[62,221–223] SVI, calculated from CI and heart rate (HR), may be a better variable for risk assessment than CI, since changes in CI may be misleading if they occur due to changes in HR.[215,216,224]

Weatherald et al. evaluated the prognostic importance of clinical and hemodynamic variables during follow-up, after initial management in PAH, in predicting death or lung transplantation (n=981) from the French PH Registry. In a multivariable model considering only baseline variables, no hemodynamic variables independently predicted prognosis. Two variables that reflect RV function, SVI, and RAP measured at follow-up were the strongest hemodynamic predictors of outcome. SVI thresholds of < 31 mL/m2 are associated with lower short term

and long-term transplant-free survival in patients with IPAH, HPAH, and drug or toxin-induced PAH, whereas a SVI > 38 mL/m2, which is near-normal, was associated with better transplant-free survival.[215] The superior prognostic utility of SVI compared to CI has been demonstrated in populations with systemic sclerosis associated PAH.[216,224]

Hemodynamic variables that reflect RV afterload such as PVR and pulmonary arterial compliance (PCa) also predict prognosis. PVR and PCa are calculated hemodynamic values that reflect the resistive and pulsatile components of RV afterload, respectively.[225] PCa is calculated from the ratio of SV to PA pulse pressure and indicates the global distensibility of the pulmonary circulation. PVR is calculated as the transpulmonary gradient (mPAP – Pulmonary Artery Wedge Pressure [PAWP]) divided by CO. Of note, PVR and PCa are inversely related to each other and linked mathematically, such that PCa decreases early in the disease process before PVR rises and PCa changes little at high PVR.[226] Changes in PCa have been associated with survival, transplant-free survival, and clinical worsening in diverse PAH populations.[227–235] In the French registry study by Weatherald et al, although PCa was predictive in the univariate analysis, it was not retained in the multivariate model and did not have greater prognostic value than SVI.[215]

Since changes in PVR and absolute values of PVR are often used in clinical practice to gauge treatment effectiveness, and since PVR remains a frequently used efficacy endpoint in early phase clinical trials, it remains a key variable to consider for individual risk assessment. The PVR obtained after initial treatment is linked to future outcomes,[215,236] though the optimal PVR threshold or target for use in risk stratification remains uncertain. In the original REVEAL score, a PVR > 32 Wood units (WU) was an independent risk factor for death,[12] though this degree of PVR elevation is rarely encountered in clinical practice. In the REVEAL 2.0 model, a PVR < 5 WU was a protective factor associated with lower mortality.[34] A meta-analysis of 21 randomized controlled trials (RCTs) and 3306 PAH patients reported that although ΔPVR and ΔCI were independently predictive of total mortality, none of the changes in hemodynamic indices was significantly related to the hospitalizations for PAH or death due to PAH in multivariate regression analysis.[237] Not surprisingly, worsening mPAP, PVR or CI were associated with more adverse clinical events.

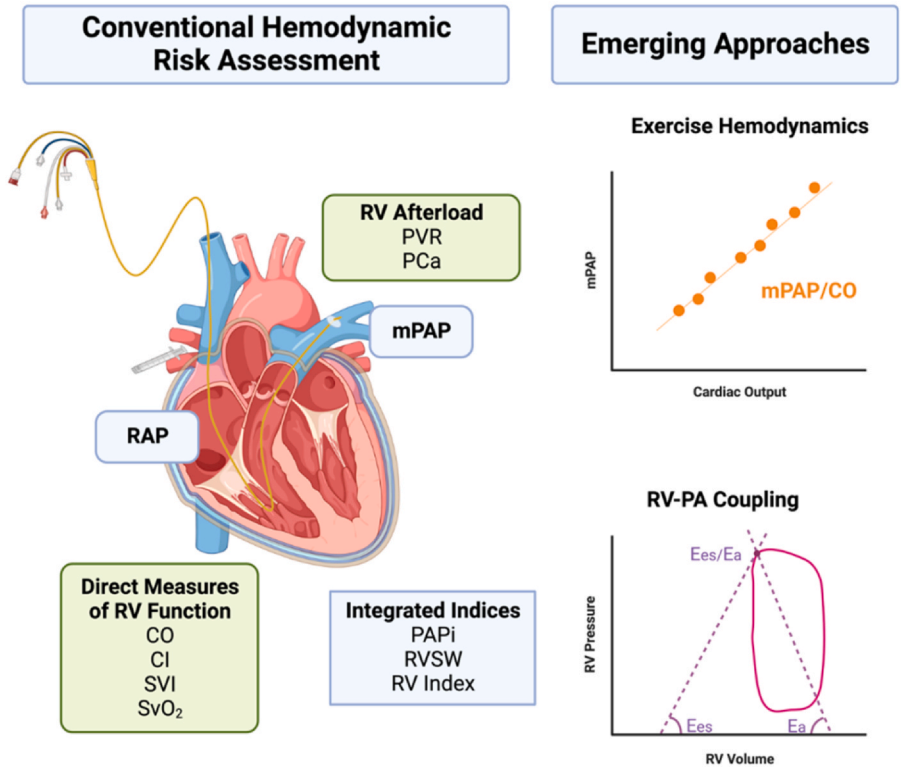
A failing RV reflects the uncoupling of the RV-pulmonary arterial unit, leading to increased RAP. As such, increased RAP remains one of the most consistent hemodynamic variables associated with prognosis, including in historical cohorts,[57] more modern cohorts including the French registry[59,215,216] and in REVEAL 1 and 2.0 scores.[12,34] Several calculated indices that incorporate elements of RV function and load have been evaluated. The pulmonary artery pulsatility index (PAPi) is a parameter calculated as the ratio of PA pulse pressure and RAP, which has been linked to prognosis in patients with left heart failure[238] but has limited study in PAH populations. Two small retrospective studies have demonstrated an association between PAPi and survival though the predictive value may largely lie in the RAP.[239,240] RV stroke work index, calculated as (SVI × (mPAP– RAP) × 0.0136) may have superior prognostic value to PAPi specifically in CTD-associated PAH.[241] An 'RV index', calculated as ((RAP × PVR)/SvO2)) was strongly associated with death or transplant in two cohorts of PAH patients, with a cut-off > 91 predicting worse outcomes[242]. Measures of ventricular-arterial coupling derived from pressure-volume loop analysis that are load-independent, such as Ees/Ea, have been linked to survival and clinical worsening in PAH, even when RVEF is preserved.[243,244] As afterload increases (Ea), contractility (Ees) must increase to maintain SV and CO. In advanced disease as the RV dilates, uncoupling occurs with a decline in the Ees/Ea. Although measurement of Ees/Ea invasively with pressure-volume conductance catheters is the gold standard for measuring RV/PA coupling, this may be less practical in routine clinical follow-up and can be approximated using non-invasive methods including CMR[245] and using the TAPSE/PASP on echocardiography.[160,161]

Provocative testing of the RV and pulmonary circulation using fluid challenges or exercise hemodynamic testing can help assess RV reserve and adaptation to stress, which could also be a useful tool for risk assessment (Figure 3).[225] Changes in CI and mPAP/CO during exercise predicted future survival in a few small studies,[246,247] but this requires considerable expertise to perform routinely in practice. In a small study of 32 patients, a CI measured after rapid infusion of saline of < 2.8 L/min/m2 was an independent predictor of clinical worsening events.[248] While potential useful to refine risk, the role of provocative testing likely requires further study to define its incremental value above conventional approaches.

Key points:

1. Hemodynamic indices that reflect right ventricular (RV) function and RV coupling to the pulmonary circulation may be better markers of prognosis and response to therapy than traditional hemodynamic variables but require further multicenter validation studies. Additionally, further research to identify thresholds associated

Figure 3 Invasive Cardiopulmonary Hemodynamics and Risk Assessment. Abbreviations: CO – cardiac output; CI – cardiac index; Ea – arterial elastance; Ees – end-systolic elastance; mPAP – mean pulmonary arterial pressure; PA – pulmonary artery; PAPi – pulmonary artery pulsatility index; PCa – pulmonary arterial compliance; PVR – pulmonary vascular resistance; RAP – right atrial pressure; RV – right ventricle; RVSW – right ventricular stroke work; SVI – stroke volume index. Created with BioRender.com.



with improved outcomes, and minimal clinically important changes with therapy for these hemodynamic indices could clarify their role in risk stratification or as endpoints in early phase clinical trials.

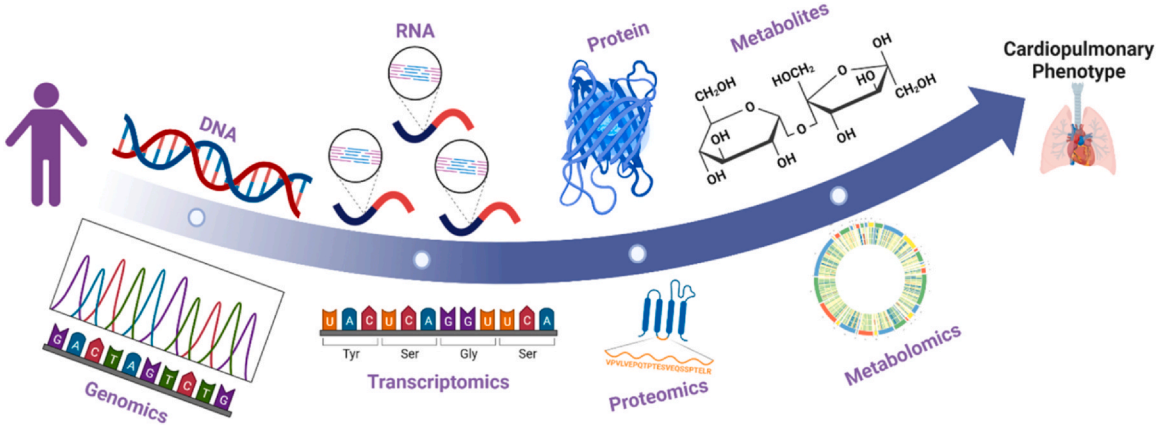
2. Hemodynamic responses to provocative challenges (fluids, pulmonary vasodilators, or exercise) during RHC can provide information about risk but are difficult to perform and standardize. Large, multicenter studies to evaluate the incremental value of hemodynamic challenges in risk assessment are needed.
3. While PVR, CI and RAP measurements have prognostic associations at baseline, SVI, SVO2 and RAP at follow-up have been associated with clinical outcomes.
4. The role of invasive hemodynamic measures of RV-arterial coupling and exercise hemodynamics in risk assessment requires further study.

2.9. Genetics

2.9.1. Genetic and genomic features of PAH risk

There are many molecular features of a biologic condition that may contribute to risk assessment in subjects with PAH, including genetic assessment of biospecimens using DNA or RNA variations, proteins, and metabolite levels. These values provide the opportunity to determine and integrate various 'omic' profiles (Figure 4). Genetic studies have shed significant insight into both disease risk and prognosis[249,250]. The 7th WSPH recommends genetic testing in several subsets of PAH (Table 6) to help estimate prognosis, carry out risk assessment in families and enable early diagnosis of asymptomatic family members, while deepening our understanding of the disease, particularly in clinical trials.[251] A recent case series by Varghese et al. reported the impact of cascade genetic testing in clinical outcomes of five distinct families with HPAH. In one case, the asymptomatic sister of a

Figure 4 Genetic and 'omics' features of PAH risk.



15-year-old male with compound heterozygous pathogenic variants in the *EIF2AK4* gene was found to have the same mutation as her brother at screening. The patient was monitored with clinical, imaging, and laboratory assessments, and was diagnosed with PH six months later. Over time, her disease progressed, ultimately requiring lung transplantation 36 months after molecular diagnosis. Other cases in the series reported also demonstrated the identification of mutations in relatives of patients with HPAH, allowing for the monitoring of asymptomatic mutation carriers, some of whom subsequently developed the disease.[252]

The estimation of prognosis makes genetic assessment appealing to incorporate into risk stratification. Unlike other variables, such as intrinsic exposures, (e.g., variations in hormone levels) or extrinsic exposures (e.g., medication or viral exposures, etc.), detectable variations in the DNA such as rare or common variants are unlikely to demonstratively change in a PAH patient according to time. One exception to this, however, is the alteration of gene expression profiles due to epigenetic changes to DNA, such as histone modifications and DNA methylation, which may occur at the cellular level,[253] as recently studied using network analyses of T cells.[254]

To date, most genetic studies related to risk assessment in PAH are confined to identification of germline rare variations (mutations) in the major known genes associated with PAH pathogenesis. Identification of a mutation in one of these genes in a PAH patient dictates that PAH be classified as a heritable condition (HPAH)[255]. While at least 16 genes have now been associated with PAH (https://search.clinicalgenome.org/kb/conditions/MONDO:0015924), approximately 75% of HPAH cases are due to mutations in the Bone Morphogenetic Protein

Table 6 Recommendations for Genetic Testing from the 7th WSPH[251]

	Symptomatic Patients		Asymptomatic Family Members	
	Pediatric	Adult	Pathogenic/Likely Pathogenic Variant in Proband Known	Pathogenic/Likely Pathogenic Variant in Proband Unknown
Types of pulmonary hypertension recommended for testing	Group 1: IPAH, HPAH, CHD, PVOD/PCH, and DT-PAHGroup 3: developmental lung disorders and congenital diaphragmatic hernia#	Group 1: IPAH, HPAH, CHD, PVOD/PCH and DT-PAH		
Type of test recommended	ES/GS, ideally including parental samples	Panel testing: follow-up with ES/GS if panel is negative in HPAH, CHD	Test for family-specific variant	Panel testing: if negative, the test is uninformative

IPAH: idiopathic pulmonary arterial hypertension; HPAH: heritable pulmonary arterial hypertension; CHD: congenital heart disease; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary hemangiomatosis; DT-PAH: drug- and toxin-associated PAH; ES: exome sequencing; GS: genome sequencing, #: genetic testing for trisomy 21 and bronchopulmonary dysplasia should be limited to patients with atypical presentation, severity or response to therapy.

Receptor Type 2 (BMPR2) gene.[256,257] Since its initial discovery over two decades ago,[258–260] *BMPR2* has been firmly established as a causative gene in up to 10–29% patients with IPAH and up to 70% of HPAH. As sequencing technology became more readily available, more than 300 mutations in *BMPR2* have been reported along with the discovery of many more rare variant mutations in other unrelated genes[249,250] including *ACVRL1*, *BMPR1A*, *BMPR1B*, *GDF2* or *BMP9*, *CAV1*, *EIF2AK4, ENG*, *KCNK3*, *TBX4, ABCC8*, *ATP13A3*, *KCNA5*, *KLF2*, *SMAD1/4/9*, *KLK1*, *GGCX* and *SOX17*[261].

Studies have shown that certain mutations not only increase the risk of developing PAH, but also affect disease severity and influence prognosis·[262] A meta-analysis of several PAH cohorts (n=1164 patients) revealed that *BMPR2* mutation carriers exhibited increased risk for composite of death or lung transplantation (hazard ratio 1·42, 95% CI 1·15–1·75; p=0·0011) and for all-cause mortality (hazard ratio 1·27, 1·00–1·60; p=0·046) in age-adjusted and sex-adjusted models comparing with non-carriers·[262] This study further observed that patients with *BMPR2* mutations are more likely to present at a younger age, manifest greater disease severity at diagnosis with higher pulmonary vascular resistance and lower cardiac index and are less likely to respond to acute vasodilator testing·As such, some PAH risk calculators, such as the REVEAL Risk Calculator, include HPAH as a risk factor for deleterious outcome.[34]

As most patients with PAH do not have evidence of these rare mutations, the value of more common genetic variants has recently been explored. In a large study of 1198 patients with PAH, a multiple-testing adjusted single-nucleotide polymorphism (rs11157866) in the G-protein alpha and gamma subunits gene was significantly associated, with a combined improvement in functional class and 6-minute-walk distance at 12 and 18 months and marginally significant improvements at 24 months.[263] Common genetic variations were also evaluated in the largest global meta-analysis across the US, Canada, and Europe.[264] Based on two separate genome-wide association studies (GWAS) and a meta-analysis of PAH from four international case-control studies across 11 744 individuals with European ancestry (including 2085 patients), a locus upstream of *SOX17* (rs10103692, odds ratio 1·80 [95% CI 1·55–2·08], $p=5{\cdot}13 \times 10^{-15}$) and a second locus in *HLA-DPA1* and *HLA-DPB1* (collectively referred to as HLA-DPA1/DPB1 here; rs2856830, 1·56 [1·42–1·71], $p=7{\cdot}65 \times 10^{-20}$) within the class II MHC region were associated with PAH risk. The *HLA-DPA1/DPB1* rs2856830 genotype further stratified survival, with median survival from diagnosis in patients with the C/C homozygous genotype was double (13.50 years [95% CI 12.07 to > 13.50]) of those with the T/T genotype (6.97 years [6.02–8.05]), despite similar baseline disease severity.[264] Both loci expand our understanding of genetic triggers of disease risk, suggesting potential roles for autoimmunity with the *HLA* locus and endothelial cell (EC) pathology with the EC-specific transcription factor, *SOX17*. While previous blinded RCT drug trials have been unable to demonstrate mortality benefit from targeting these factors, these genetic data implicate the ability to drive precision medicine in PAH for new clinical trial design evaluating mortality as a primary outcome by incorporating knowledge of patients at highest genetic risk.

Linking precise genetic variations to PAH outcome has yet to be fully implemented into risk assessment. Of note, particularly for pediatric PAH cases, there is growing recognition of T-box transcription factor 4 (TBX4) gene mutations, with mutations in this gene the second-most common finding for HPAH cases; but, associations with risk of deleterious outcomes remain an area of study.[265] Challenged by low numbers given the relative rarity of PAH as a disease entity, efforts to identify common genetic variations in the genome that associate with risk and resilience to PAH decompensation have yet to be validated and implemented on a clinical basis. However, a tactic to pair genetic variations with downstream variations in RNA or protein expression has resulted in some promising variations that remain under study. For example, given work demonstrating associations of circulating levels of the angiostatin protein endostatin with hemodynamics and survival in PAH,[142,143,266] assessment of common variations in that gene (COL18A1) that may influence protein expression has been pursued.[267] That work does suggest that severity of PAH and its trajectory over time may be influenced in part by genetic variation in the COL18A1 gene, but additional studies are needed. Similar explorations have been conducted for many years related to suspected pathogenic contributors to PAH such as serotonin signaling and sex hormones in PAH, but all require additional study.[268,269] As a result, as with proteomic profiling, while intriguing to consider the insertion of genetic variation into current risk assessment approaches, additional work is needed including biologic mechanistic explorations and studies in large numbers of patients.

Key points:

1. Mutations of the *BMPR2* gene are associated with worse outcomes in patients with PAH. These mutations are present in most patients with HPAH. For this reason, the REVEAL 2.0 risk model assigns a higher score to patients who belong to this subset (HPAH).

2. The widespread implementation of genomics into risk assessment in PAH has yet to occur. The rarity of this disease makes it difficult to identify and validate genetic mutations associated with greater risk of mortality.

2.10. Ancillary testing

2.10.1. Pulmonary function testing

Lung function testing may provide early clues to the presence of pulmonary vascular disease. The early hallmark of the disease is impaired exercise capacity, despite a preserved resting hemodynamic profile. This is mediated through complex phenomenon, including increased dead-space ventilation, increased ventilatory requirement and a decreased CO_2 response to exercise.[270]

The role of spirometry has been examined thoroughly as a potential tool to define risk in PAH. Airway obstruction has been described in several studies, based on a forced expiratory volume in 1 s / forced vital capacity (FEV1/FVC) ratio of less than 70%.[271] Recent registry data suggests that even mild obstruction in the context of normal chest imaging may have a worse prognosis than PAH without flow limitation,[272] though spirometry is not featured in any risk predictors in common use.[6] In general, significant obstruction or restriction is not consistent with PAH, however, this might carry more significance now as more and more inhaled therapies using dry powder inhalation (DPI) devices are being tested in PAH.[273] One may hypothesize that patients with intrinsic airway obstruction might have difficulty with the drug delivery and perhaps affect the drug efficacy, but, this will need prospective studies for validation.

In contrast, depressed diffusion capacity for carbon monoxide (DLCO) has long been recognized to be a common feature of PAH.[220,274,275] Further, depressed DLCO is an independent predictor of death in patients with PAH[275] with a threshold of about < 45% predicted generally accepted as a predictor of worse outcome.[272,276,277] PAH patients with depressed DLCO may represent a unique "lung phenotype" characterized by older age and more frequent history of tobacco use.[278] Thus, there appears to be an emerging consensus that low DLCO is a feature of most patients with PAH, but severely depressed DLCO is associated with worse prognosis. A recent analysis by Olsson et al. examined changes in DLCO in 35 patients who participated in the sotatercept clinical trials, from baseline to week 24. Patients who received active drug exhibited a change of 4% (1 to 6) in DLCO, compared to −4% (−6 to −2) in the placebo group. These findings call for further analyses in larger cohorts.[279]

Key points:

1. Concomitant airway obstruction may be prognostic but needs larger multicenter studies for validation.
2. Further evaluation of low DLCO as an indicator of PAH disease severity, target of therapy or prognostic factor is needed.
3. Newer antiproliferative therapies like sotatercept have been associated with improvements in DLCO when compared to placebo.

3. HISTORICAL PERSPECTIVES ON MULTI-RISK FACTOR ASSESSMENT

The management of patients with PAH is increasingly complex as more therapies have become available. In addition, determining accurate prognosis is challenging, as more aggressive multi-drug treatments and promising novel reverse remodeling strategies have the potential to change the natural history of PAH in the modern treatment era. As a result, great effort has gone into developing risk scores capable of accurately characterizing patient outcome and response to therapies above what individual risk components described earlier can do on their own. If perfected, such risk assessment tools could facilitate early escalation of treatment in patients at risk for deterioration and could reinforce treatment strategies in stable or improving patients. Over the past decade, several risk stratification tools were created from large patient registries.[24,33,59,60,280] Data obtained from these registries have become the basis for understanding features associated with PAH mortality.[7,12,23,33,74,110] Risk prediction tools in PAH provide a consistent approach for evaluating patients' clinical status and prioritizing discussions among healthcare providers, patients, and their families. These discussions aid in clinical decision-making and advanced care planning. Further, they optimize the treatment strategy based on risk assessment at diagnosis and subsequent follow-up. Lastly, mortality risk tools using validated objective parameters in

conjunction with clinical judgment could provide a comprehensive evaluation for patients with PAH.[33] In the following sections, we will review the evolution of these tools, their relative similarities and differences and provide a framework for their use in the clinical environment.

The first attempt to establish a predictive equation to determine prognosis was derived from the National Institute of Health (NIH) registry of patients from the 1980's.[29] This registry included 187 patients from several US centers with IPAH, HPAH, and anorexigen-related disease, then defined as 'primary PH'. Analysis of this registry resulted in the formulation of a survival estimate equation based principally upon hemodynamic factors derived from RHC including CI, RAP and mPAP. The equation did not incorporate other clinical parameters such as functional class, biomarker response (such as NT-proBNP) or exercise tolerance, which are now recognized as critical to the overall risk assessment of the patient. Furthermore, derivation of this equation was based on a population of patients who were not exposed to the current era of disease targeted therapy, and therefore the equation may not be as relevant to more contemporary populations. Indeed, a study looking at the use of this NIH registry equation in 2012 showed that it underestimated survival in the current era. This also led to the derivation and validation of the PH connection equation from a single center in Chicago in 2012; though a refinement of the original NIH equation, it remained focused on hemodynamics. Nevertheless, this updated equation showed a reasonable ability to predict outcomes, and agreed with another prognostic equation developed from the French registry.[281]

The next step in risk assessment emerged from the need for a treatment approach to determine when to escalate therapy. Individual risk improvement and goal setting, known now as "goal directed therapy" for pulmonary hypertension emerged, which incorporated clinically relevant endpoints and time specific goals to patient assessment and treatment escalation. In a seminal paper form Hoeper et al., a prospective cohort of PAH patients were compared to a historical cohort from the same PH center to determine if goal directed therapy improved outcome.[282] The results of this study demonstrated that goal directed addition of therapeutics improved hard clinical outcomes (death, lung transplantation, and need for intravenous therapy). This launched a clinical paradigm that was used by many centers for a few years until the maturation of contemporary risk stratification tools emerged.

In 2006, a sentinel article by McLaughlin and McGoon[283] first advocated the incorporation of several clinical factors, as opposed to one or two into the decision-making process. Their original risk table included "lower" and "higher" risk estimates, instead of discrete cut-offs for FC, BNP, 6MWD, right atrial pressure, cardiac index, pericardial effusion, and evidence of RV dysfunction clinically and by echo. Based on the presence of lower or higher risk, suggestions on therapeutic avenues were made. They concluded that the goals of therapy should include improvement to WHO-FC I or II and improvement in 6MWD (to ≥380 m).

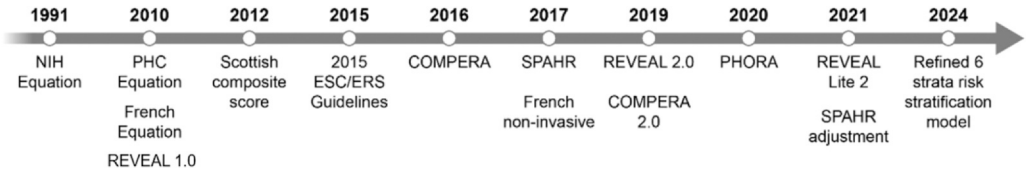
In 2010, the REVEAL risk equation(284) was introduced to evaluate prognosis in PAH followed by a simplified risk calculator in 2012.[33] Also in 2010, the investigators from the French national registry reported on survival metrics in a population of Group 1 patients and found that the combination of female sex, 6MWD, WHO-FC, RAP and CO were able to predict survival with an estimated C statistic of 0.57 (95% CI, 0.29 to 0.82).[19] In 2015, the ESC and the ERS jointly published a risk factor assessment table in the Guidelines for PAH Diagnosis and Treatment.[7] From 2017 the COMPERA or ESC/ERS 3-strata system,[6] the French PH Registry (FPHR) number of low risk variables,[59] and the Swedish PAH Registry (SPAHR) scoring system arose in 2017.[24,285] The COMPERA, FPHR, and SPAHR risk tools rely on cut-offs of variables defined by the 2015 ESC/ERS guidelines. These tools (described in detail in ensuing sections) continued to improve as investigators learned more about the weight of each metric in assessing disease prognosis and modified versions of these initial risk assessment tools were developed such as the REVEAL 2.0 Risk Score[34] and REVEAL lite 2[117] in 2019, the Bayesian derivation of REVEAL 2.0 in 2020,[286] followed by the updated SPAHR model in 2021,[25,285] COMPERA 2.0 (ERS/ECS 4-Strata) in 2022,[75] and French 6-strata in 2024.[287] (Figure 5).

4. CONTEMPORARY RISK SCORES

4.1. United States scoring systems

The original REVEAL equation was statistically derived in 2010[284] from the multi-center REVEAL registry, which enrolled patients with PAH from all different Group 1 subgroups in the USA. This tool developed a prognostic risk stratification ordinal score between 0 to 21 by taking into account 12 statistically weighted modifiable (e.g. systolic blood pressure, heart rate, 6MWD, WHO-FC, natriuretic peptide levels, renal insufficiency, DLCO, hemodynamics

Figure 5 Timeline of development of risk stratification tools.



like RAP and PVR and presence of a pericardial effusion) and non-modifiable risk factors (eg. age, sex and PAH subset).[33] Although this tool was developed predominantly in prevalent patients, it was also shown to risk stratify in a large group of newly diagnosed (less than 3 months) patients as well. Through further refinement of the REVEAL population and adding important new clinical variables such as hospitalization within 6 months and eGFR, as well as adding more cut points for 6MWD and natriuretic peptide levels, the REVEAL 2.0 score was developed.[34]

Subsequently, the REVEAL Lite 2 score was derived because of the need for a rapid clinical score consisting of only modifiable factors to be used in daily encounters and in the absence of invasive or other more expensive metrics. REVEAL Lite 2 uses 6 parameters from REVEAL 2.0: 6MWD, FC, BNP, blood pressure, HR and renal function, and predicts with "good discrimination" (c-score > 0.7), although not as good as the parent REVEAL 2.0 (c-score 0.76).[117] Finally, in 2020, a Tree Augmented Naïve Bayes model (titled PHORA)[286] was conceived to predict one-year survival in PAH patients included in the REVEAL registry, using the same variables and cut-off points found in REVEAL 2.0. Bayesian networks (BN) are highly efficient and sophisticated algorithms that can assimilate complex medical data in a time-efficient manner, thereby acting as a tool for predicting clinical outcomes based on learned information. Unlike traditional cox-derived algorithms, they can account for dynamic, non-linear interactions between multiple variables and their interdependency in influencing outcomes at various time points.[288] The PHORA model was validated internally (within the REVEAL registry) and externally (in COMPERA and PHSANZ registry) with an AUC of 0.80 for predicting one-year survival, which was an improvement over REVEAL 2.0.

4.2. European scoring systems

The Scottish composite score was developed in 2012 in the UK. This score incorporated multidimensional data for patients (age, sex, diagnosis, RAP, CO and 6MWD), and performed well when compared to both the PHC and French equations.[21] This effort also showed that risk stratification could be effective across geographical boundaries. Because of these initial survival-based equations, focus changed from purely identifying survival outcomes to the development of multi-parametric risk scores which could change in real time and measure response to treatments; this would allow a much more personalized approach to patient care. Development of these scores varied from derivation by expert consensus to more statistically robust scores and included different forms of PAH and more extensive clinical parameters.

In 2015, the ESC/ERS jointly published guidelines that outlined key parameters in a multi-dimensional table (Table 4), like that proposed by McLaughlin and McGoon in 2006 to assess the risk of deterioration in patients with PAH. This comprehensive table included parameters with discrete cutoffs and focused on physiological parameters (6MWD, WHO-FC), the state of the RV (imaging and biomarkers) and disease progression (clinical features, invasive hemodynamics). This table was designed to give an overall prognostic outlook via stratification into one of 3 categories – low, intermediate or high, corresponding to estimates of mortality at 1 year.[7] This table and approach were later validated in 2016 and 2017 in several large registries: the Swedish, French and COMPERA registries, and further refined into specific tools using 6–11 specific variables.[24,59,60]

In 2017, a French tool was developed that examined whether a patient was low-risk or not using the absence or presence of 3–5 low-risk characteristics based upon the 2015 ESC/ERS PH guidelines table described above, in a cohort of incident patients (predominantly IPAH). They found that at baseline and particularly at follow up, the number of low-risk characteristics was closely associated with outcome. Particularly notable was a sub cohort of patients at follow up with normal BNP or NT-proBNP values and who also achieved WHO-FC I/-II- and 6MWD > 440 m, who had a 5-year survival was 97%. The Swedish and COMPERA tools took a different approach and

classified patients into low, intermediate, or high-risk categories based on cut-off values proposed in the ESC/ERS guidelines. For COMPERA, six variables (WHO-FC, 6MWD, natriuretic peptide levels, SVO2, RAP, and CI) were used, whereas eight variables were used for the SPAHR model (WHO-FC, 6MWD, NT-proBNP, hemodynamics, and echocardiographic variables [RAP, and presence of pericardial effusion]). In each, variables were graded 1–3 (1: low risk, 2: intermediate risk and 3: high risk). For each patient, the sum of all grades was divided by the number of available variables and rounded to the nearest integer to define the risk group (Fig. 7).

In 2019 the COMPERA 3-strata score was widened to a 4-strata system, which utilized only three variables (6MWD, WHO-FC, and natriuretic peptide levels) and separated their intermediate category into intermediate high and low. Evaluation of over 4000 patients has determined this allowed better discrimination within their defined intermediate group, allowing more accurate and sensitive assessment of the response to treatments at follow up.[75] A different adjustment was made to the updated SPAHR tool in 2021[285] using cut-off values for WHO-FC, 6MWD, NT-proBNP, RA area, mean RAP, pericardial effusion, CI and/or SvO2, as defined in the "risk table" of the 2015 ESC/ERS guidelines. Patients in the intermediate risk group in an exploratory analysis were further divided into a low-intermediate (risk score 1.5–1.99) and a high-intermediate (risk score 2.0–2.49) risk group.[25,285]

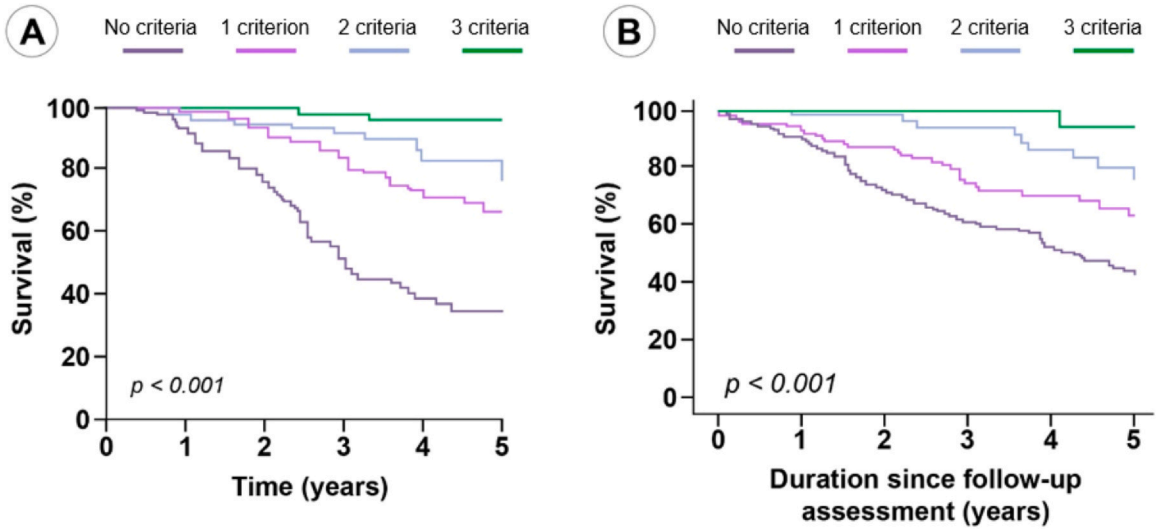
5. CONTEMPORARY RISK STRATIFICATION TOOLS: ADVANTAGES AND OPPORTUNITIES

5.1. French approach of risk stratification in PAH

The French approach to risk stratification focused on the low-risk profile. It aimed to determine how many low-risk variables were needed to define a low-risk profile and to provide a target zone for treatment goals.[59] Importantly, this approach was not designed to segregate non low risk patients into intermediate or high risk. This tool was studied in a large cohort of 1017 incident patients with IPAH, HPAH, and drug-associated PAH assessed by WHO-FC, 6MWD and RHC at both baseline (i.e. time of PAH diagnosis) and at a follow-up visit performed within the first year after diagnosis. Transplant-free survival was analyzed according to the number of four available low-risk variables (WHO-FC I or II, 6MWD > 440 m, RAP < 8 mmHg and CI ≥2.5 L/min/m^2) present at baseline and achieved at follow-up. In univariable Cox regression analyses at both baseline and follow-up all four variables were associated with outcomes. However, only a baseline 6MWD ⩽440 m independently predicted death or transplantation while all four variables were independently associated with survival when analyzed at follow-up. At first follow-up, patients achieving 4 low-risk criteria had less than 1% risk of death at 1 year and a 94% 5-year transplant-free survival rate. In contrast, 5-year survival was 81% in patients achieving 3 low-risk criteria and 34% in those who failed to achieve any low-risk criteria.[59] Interestingly, there was no significant difference in survival according to which three of the four criteria were achieved within the group achieving three low-risk criteria. Another interesting finding was that the mortality risk was associated with the number of high-risk criteria (NYHA IV, 6MWD < 165 m, RAP > 14 mmHg, CI < 2.0 L/min/m^2) in patients who did not achieve any low-risk criteria.[59]

The additive value cardiac biomarker criteria defined by a BNP < 50 ng/L or a NT-proBNP < 300 ng/L to determine a low-risk status was examined in the subset of 603 patients for whom these variables were available at follow-up.[59] The low-risk BNP/NT-proBNP cut-offs were associated with transplant-free survival in univariable and multivariable analyses whereas hemodynamic variables obtained by RHC (RAP and CI) were no longer independently associated with outcomes in the multivariable model. The number of non-invasive low-risk criteria (FC I–II, 6MWD > 440 m, BNP < 50 ng/L or NT-proBNP < 300 ng/L) achieved at follow-up strongly predicted transplant-free survival (Figure 6). Nineteen percent of patients met all these three non-invasive low-risk criteria and had a 97% 5-year transplant-free survival rate.[59] This non-invasive approach has been validated in 579 patients with IPAH from the COMPERA registry.[289] The 5-year transplant-free survival rate was 95% in the 9% of patients who achieved the three non-invasive low-risk criteria.[289] The proportion of patients achieving all three non-invasive low-risk criteria was higher in a Swiss real-life cohort of PAH in which 33% of prevalent PAH patients achieved those criteria at follow-up.[290] This non-invasive approach of risk is useful in clinical practice, it allows the identification of patients at very low risk of death or lung transplantation and may obviate the need for routine invasive hemodynamic follow-up assessment in selected patients. In patients achieving the three non-invasive low-risk criteria at follow-up (FC I-II, 6MWD > 440 m, and BNP < 50 ng/L or NT-proBNP < 300 ng/L). This risk approach was subsequently applied and

Figure 6 Transplant-free survival according to the number of noninvasive low-risk criteria (functional class I–II; 6MWD > 440 m; BNP < 50 ng/L or NT-proBNP < 300 ng/L) achieved at first re-evaluation, A) in the French PH Network Registry (A panel, n=603)[59]; B) in the COMPERA cohort (B panel, n=579).[289]



validated in two large cohorts of patients with PAH associated with systemic sclerosis.[216,291] As with patients with IPAH, the more low-risk criteria were achieved, the better the survival.

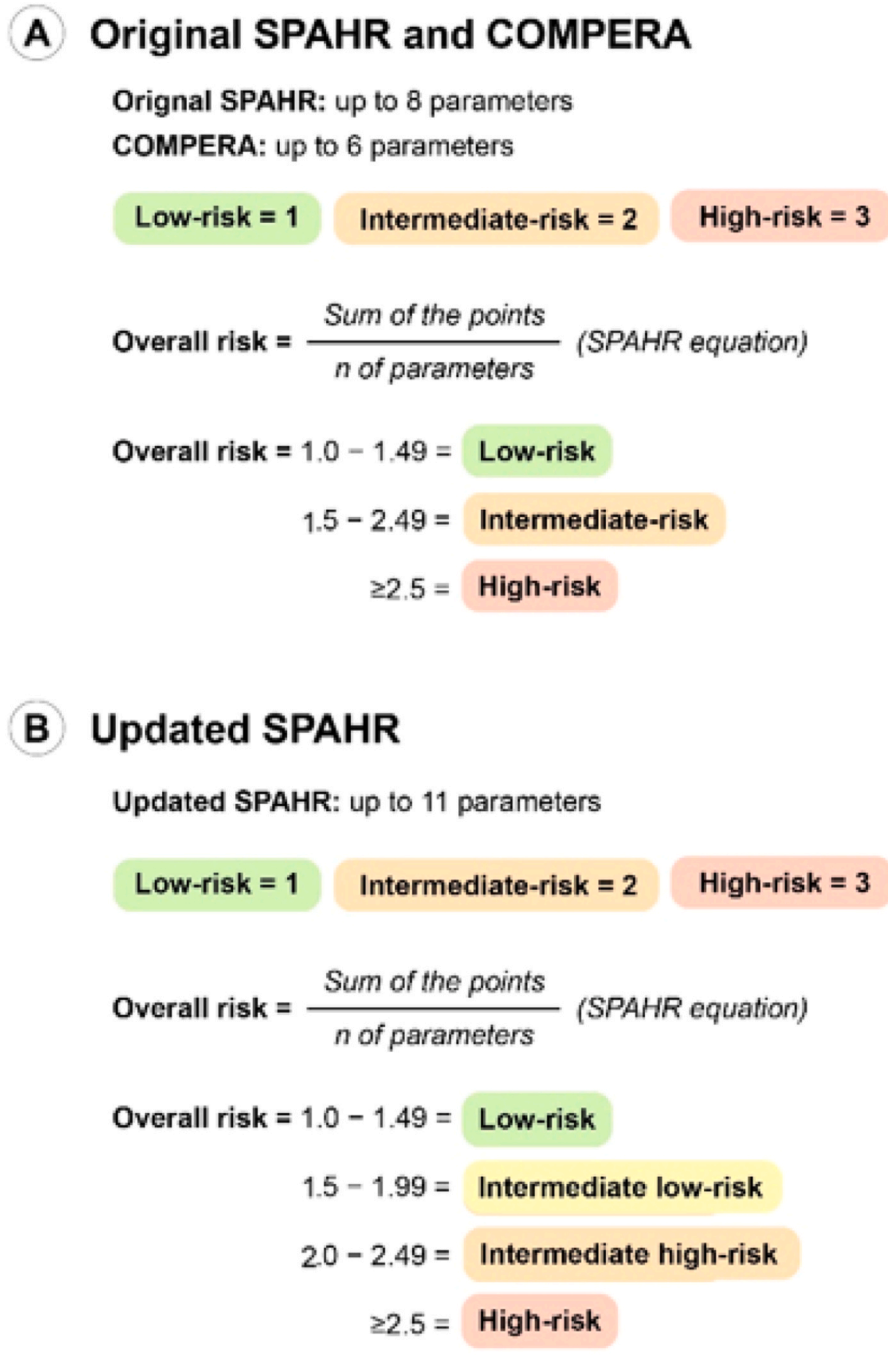
In summary, the non-invasive approach based on FC, 6MWD and biomarkers is an easy way to identify PAH patients with low risk, but those found at not low risk need to be reevaluated with a more discriminatory tool to confirm "non low risk status" to prevent overutilization of unnecessary therapeutics.

5.2. COMPERA risk tools

The 3-strata model as per the 2015 ESC/ERS guidelines classified patients into low, intermediate, or high risk with corresponding estimated 1-year mortality rates < 5%, 5–10%, or > 10%, respectively. Risk was to be determined from a multivariable table with cut-off values derived from both expert opinion and medical literature.[7] Once these guidelines were published, several registry studies attempted to validate and structure this table into a usable clinical model. The COMPERA models used specific variables and an arithmetic approach, as described previously.[24,60] The studies from COMPERA showed that abbreviated versions of the ESC/ERS risk stratification tool provided fair to good discrimination (C-index 0.65 to 0.75) in the long-term survival predictions, when assessed at baseline and – even more so – at first follow-up, respectively. Changes in risk from baseline to first follow-up were also importantly associated with changes in long-term survival.[24,60] In addition, the COMPERA analysis found that at baseline, WHO FC, 6MWD, BNP/NT-proBNP and SvO_2 but not RAP and CI were independent predictors of survival. At first follow-up, WHO FC, 6MWD and BNP/NT-proBNP, but none of the hemodynamic variables were independently associated with survival. The authors noted that the latter finding had to be interpreted with caution as there was an abundance of missing hemodynamic values at follow-up.[60] Nevertheless, the observation that WHO FC, 6MWD and BNP/NT-proBNP were more valuable than hemodynamics as outcome predictors and agreed with findings from the French registry and REVEAL.[59,117] The lower baseline discrimination index of COMPERA also resulted in a less granular and disproportionately large number of patients in the intermediate risk group.

In order to provide more granularity within the intermediate risk category, the COMPERA investigators developed a 4-strata model using the same calculation strategy as for the original 3-strata model, refined cut-off values to distinguish between intermediate-low and intermediate-high risk (Table 7).[75] This model was tested on 1655 patients with baseline data and 1414 with data at first follow-up. The authors showed that the 4-strata provided good discrimination of long-term survival across the 4 risk strata, especially at follow-up. Compared to

Figure 7 Calculation of risk scores using the original and updated SPAHR risk stratification models[24].



the 3-strata model, the 4-strata model was more sensitive to changes in risk from baseline to first follow-up, and such changes were associated with long-term outcomes.[75]

A companion paper from the French PH registry, which was based on 2879 patients at baseline and 2082 patients at first follow-up, confirmed and extended these findings showing that the predictive value of the 4-strata model was significantly higher than that of the 3-strata model (baseline, C Index 0.67 with the 4-strata model compared to 0.63 with the 3-strata model ($p < 0.001$); at first follow-up, the C Index improved to 0.73 with the 4-strata model compared to 0.69 with the 3-strata model ($p < 0.001$).[292] The objective of PAH therapy remains

Table 7 4-Strata Risk Prediction Tool[75]

Points Assigned	1	2	3	4
FC	I or II	-	III	IV
6MWD	> 440 m	440–320 m	319–165 m	< 165 m
BNP/NT-proBNP	< 50 ng/L < 300 ng/L	50–199 ng/L300–649 ng/L	200–800 ng/L650–1100 ng/L	> 800 ng/L > 1100 ng/L

Based on the criteria shown in the table, each variable is graded from 1 to 4. The mean is calculated by dividing the sum of all grades by the number of variables and rounding to the next integer. 6MWD: 6-minute walk distance; BNP: brain natriuretic peptide; FC: functional class; NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

achieving and maintaining a low risk profile. Both the COMPERA and the French study reinforced this treatment objective as the long-term survival of patients reaching a low risk profile at first follow-up was significantly better than that of patients who reached an intermediate-low risk profile (Table 8).[75] In a subsequent paper from the COMPERA registry,[293] they analyzed the effect on discrimination when variables were missing in a cohort of 1976 patients. At baseline with all three variables, the C Index was 0.63. When one variable of the three was missing the C-Index ranged from 0.60 to 0.64. At follow up with all three parameters, the C Index was 0.69. When one variable of the three was missing the C-Index ranged from 0.67 to 0.70.

A recent analysis by Boucly et al.[287] further refined the COMPERA 4-strata model into a 6-strata one by incorporating two hemodynamic parameters. They performed an analysis on 1240 patients enrolled in the French PAH Registry who had baseline and first follow-up RHC, and identified hemodynamic variables significantly associated with transplant-free survival in each risk status. They did not find any additive value of any

Table 8 Observed 1-, 3- and 5-year Survival Rates From Baseline and First Follow-up with the 4-Strata Risk Prediction Tool[75,292]

Observed survival	1-year	3 years	5 years
COMPERA baseline			
Low	100%	89%	83%
Intermediate-low	98%	86%	79%
Intermediate-high	91%	62%	50%
High	78%	47%	28%
French baseline			
Low	98%	89%	75%
Intermediate-low	93%	81%	65%
Intermediate-high	86%	63%	44%
High	75%	45%	31%
COMPERA first follow-up			
Low	99%	91%	83%
Intermediate-low	97%	82%	67%
Intermediate-high	91%	63%	47%
High	78%	48%	33%
French first follow-up			
Low	97%	89%	81%
Intermediate-low	94%	75%	57%
Intermediate-high	81%	50%	31%
High	65%	28%	13%

hemodynamic parameters for those who achieved low risk or stayed in high risk on their first follow up. However, for the intermediate low and intermediate high-risk statuses, SVI and SVO2 were significantly associated with transplant free survival. Thus, the authors incorporated these two variables (SVi > 37mL/m^2 and/or SvO_2 > 65%) to further refine the intermediate risk group and achieved a 6-strata model that had a better prognostic performance (AUC: 0.81, c-index: 0.74) than the 4-strata model (AUC: 0.79, p=0.009, c-index: 0.72).[287]

5.3. SPAHR risk stratification scores in PAH

The original SPAHR three-strata model was first described by Kylhammar et. al.[24] utilizing the SPAHR, and subsequently adopted by Hoeper et al utilizing COMPERA.[24,59,60] The SPAHR three-strata model used specific variables and an arithmetic approach to categorize patients into low, intermediate, or high risk for one year mortality, based on thresholds in the 2015 ESC/ERS guidelines, as previously described (Table 4, Figure 7).[24] In the original SPAHR/COMPERA model, based on the SPAHR-equation, up to eight and six parameters were utilized by the SPAHR and the COMPERA registry studies, respectively.[24,294] The new updated SPAHR three-strata model, created to allow sub-division of the large intermediate risk group, is based on that the calculated mean is rounded off according to modified thresholds for the intermediate risk group (1.5–1.99=intermediate-low risk, 2.0–2.49=intermediate-high risk), thus separating the risk categories into four separate groups.[285] The updated SPAHR three-strata model, with divided intermediate risk, is still defined as a three-strata model, as it like the original SPAHR model, is based on the parameter thresholds for low- intermediate- and high risk. However, it uniquely allows separation of the risk score into four separate risk-groups (low-, intermediate-low-, intermediate-high-, and high risk) (Figure 7), all with different one-year survival rates.[285] To further facilitate risk assessment in clinical practice, a comprehensive internet-based risk score calculator (https://www.svefph.se/risk-stratification) has subsequently been established.[25,295]

5.4. The US REVEAL registry-based risk stratification

The REVEAL risk calculators were derived and validated from the REVEAL registry (Table 9).[296] The REVEAL analyses included both incident and prevalent patients and the risk calculator includes both modifiable and non-modifiable variables. The REVEAL risk scores are the only scores in which variables are weighted to reflect the hazard ratios found in the analysis of association with outcomes. Since PAH is a complex disease in which

Table 9 REVEAL Scoring Methods[374-376]

	REVEAL 1.0					REVEAL 2.0			REVEAL Lite 2		
Development	Benza et al. (2010) (12)					Benza et al. (2019) (34)			Benza et al. (2021) (117)		
Category	Low Risk	Average Risk	Moderately High Risk	High Risk	Very High Risk	Low Risk	Intermediate Risk	High Risk	Low Risk	Intermediate Risk	High Risk
1-year Survival	1-year survival					Estimated Mortality at 1 year, % (95% CI)			Estimated Mortality at 1 year, % (95% CI)		
	>95%	90% to >95%	85% to <90%	<85%	<70%	1.9 (1.1-2.7)	6.5 (4.7-8.4)	25.8 (22.7-28.9)	2.9 (1.8-3.9)	7.1 (5.4-8.8)	25.1 (21.9-28.4)
Validation	**Prospective:** Benza et al. (2012) (33) **Retrospective:** Cogswell et al. (2012) (374) Ling et al. (2012)(375) **Post-hoc analysis:** PATENT-2 (2018) (298)					**Retrospective:** Anderston et al. (2020) (301) Spilimbergo et al. (2023)(306) Fadah et al. (2023)(376) **Post-hoc analysis:** FREEDOM-EV (2022) (9) GRIPHON (2020) (334) PATENT (2021) (302)			**Retrospective:** Spilimbergo et al. (2023) (306) **Post-hoc analysis:** FREEDOM-EV (2022) (9) PATENT (2022) (303)		

outcome and treatment responses are dependent on multiple factors, the inclusion of more variables and the statistical weighting of these variables improves the precision of this risk prediction tools over others. The REVEAL scores perform equally well in both incident and prevalent patients, and improvement in risk score predicts improved outcome.[12,15,297] It has been applied to data from randomized clinical trials and is predictive of outcome,[298] and provides meaningful outcome predictions in an analysis of other PH groups.[299,300]

The REVEAL 2.0 revision of the calculator utilized data from the subset of patients entered in REVEAL who survived for at least one year, and thereby incorporated hospitalizations within the preceding 6 months as an additional risk variable.[16] It also replaced the more subjective renal insufficiency with estimated glomerular filtration rate and established updated cut points for the other variables. REVEAL 2.0 demonstrated good discrimination of risk (c-statistic 0.76) at baseline and predicted clinical worsening as well as mortality in patients who were followed greater than 1-year (Figure 8). Sensitivity analysis also demonstrated good performance in more recently diagnosed patients.

REVEAL 2.0 was validated in Australian and New Zealand PAH registry with good discrimination. In a mixed cohort of 1011 incident and prevalent patients, REVEAL 2.0 model discriminated risk with C statistics of 0.74. When applied for incident cases only, the C statistics was 0.73. The three category REVEAL 2.0 model demonstrated robust separation of 12- and 60-months survival estimates (all risk category comparison $P < 0.001$).[301] REVEAL 2.0 was also validated in the COMPERA registry.[286] Multiple post hoc analyses from the patients enrolled in the clinical trials have also independently validated REVEAL 2.0. In the pivotal riociguat trials, PATENT 1 and PATENT 2, REVEAL predicted, long term outcomes, treatment responses and clinical worsening free survival.[302] Importantly, investigators were able to demonstrate that dynamic changes in survival were associated with changes in score. As an example, in the PATENT trial, a 1-point difference in REVEAL Lite 2 score at PATENT-1 baseline or Week 12 was associated with 21% and 24% reductions in the relative risk of death in PATENT-2, respectively.[303] In another post hoc analysis[304] of the pooled data from the TRIUMPH[305] and BEAT studies, REVEAL 2.0 calculator appeared to predict short-term clinical change in the functional class III/IV population. Another study[306] from southern Brazil PAH registry, both REVEAL 2.0 and REVEAL lite 2 predicted mortality.

As described earlier, REVEAL lite 2[117] is an abridged version of REVEAL 2.0 using six modifiable and noninvasive variables (Figure 9). REVEAL Lite 2 approximates REVEAL 2.0 at discriminating low, intermediate, and high risk for 1-year mortality in patients in the REVEAL registry. The model indicated that the most highly predictive REVEAL Lite 2 parameter was BNP/NT-proBNP, followed by 6MWD and FC. Even if multiple, less predictive variables (heart rate, SBP, eGFR) were missing, REVEAL lite 2 still discriminated well (C-Index > 0.7) among risk groups. REVEAL lite 2 utilizes a smaller number of noninvasive clinical variables thus making it user friendly in every day clinical use compared to its predecessor. Recently REVEAL Lite 2 was validated in the FREEDOM-EV trial to predict future clinical worsening among the trial participants.[9] Early improvement in REVEAL

Figure 8 Pulmonary Hypertension Society of Australia and New Zealand cohort estimated 60-month survival from 1y stratified by Registry to Evaluate Early and Long-Term PAH Disease Management 2.0 risk scores.[301] Reprint permission received from the publisher.

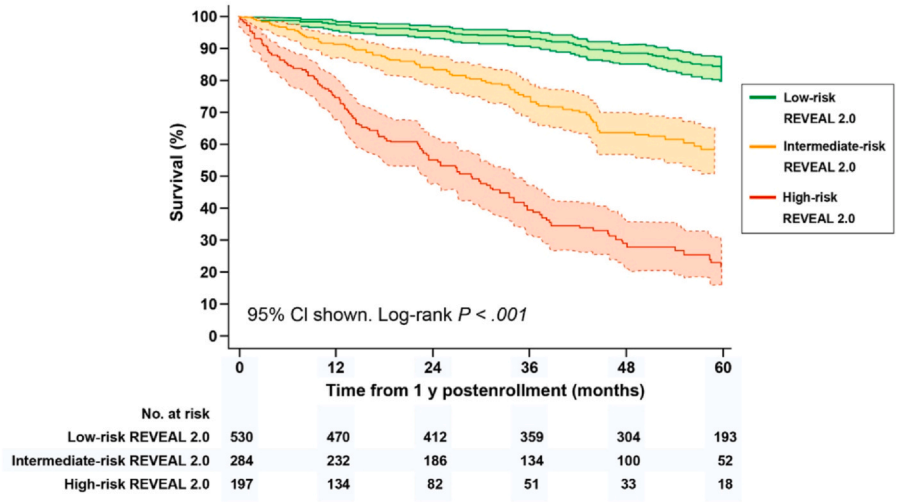
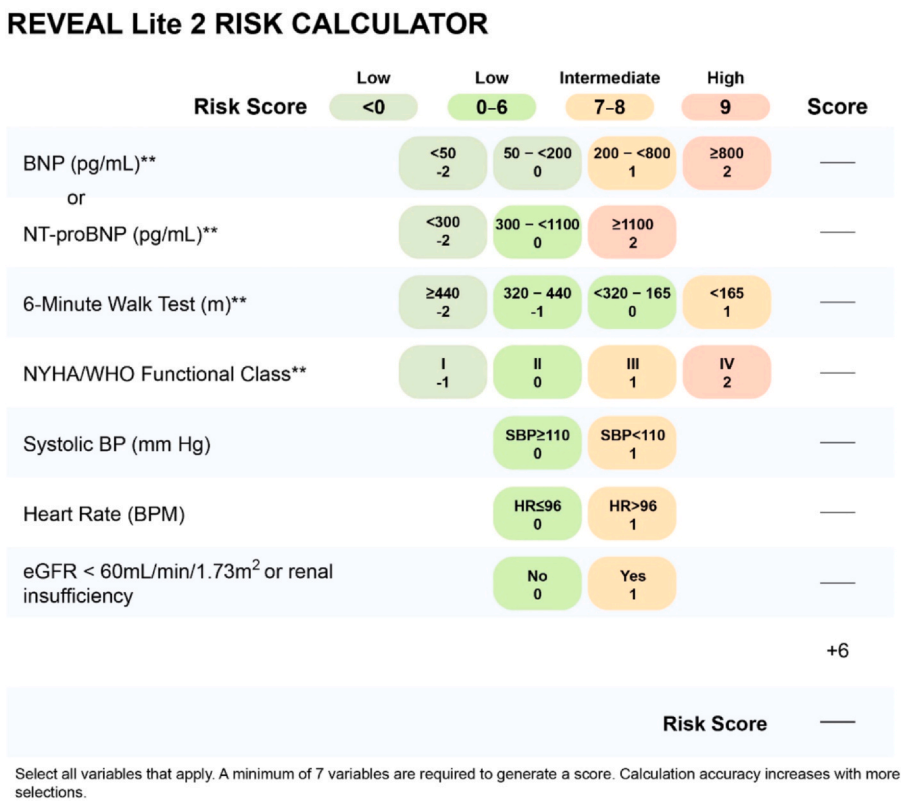


Figure 9 REVEAL Lite 2 calculator.[307] Reprint permission received from the publisher.



lite 2 score within 6 weeks predicted outcomes at week 24. This highlights the potential of risk scores to be surrogate for clinical worsening. Like REVEAL 2.0, changes in score correlated incrementally with changes in survival. As an example, in the Freedom EV trial, compared to baseline, a 1-point decrease in score at Week 12 predicted a 62% decrease in the relative risk of clinical worsening (hazard ratio (HR) 0.38, CI 0.32, 0.45, $p < 0.001$). For REVEAL Lite 2, a 1-point decrease in score at Week 12 predicted a 59% decrease in the relative risk of clinical worsening (HR 0.41, CI 0.34, 0.48, $p < 0.001$). We have seen similar association in the GRIPHON trial, where across all timepoints, for every 1-point *difference* in risk score, MME (time to first morbidity/mortality event) risk increased by 45% ($P < 0.0001$), and for every 1-point *increase* in risk score from baseline, MME risk increased by 68% ($P < 0.0001$).[307]

As noted earlier, PHORA is a Bayesian derivation of the REVEAL 2.0 calculator. Simply converting REVEAL 2.0 to a Bayesian network (PHORA predictive algorithm, e-Figure 1) markedly enhanced discrimination over the parent calculator.[286] The AUC of 0.80 for predicting one-year survival for PHORA indicated improved discrimination in predicting mortality over REVEAL 2.0 (0.76 [95% CI, 0.74– 0.78]) and REVEAL 1.0 (0.71 [95% CI, 0.68–0.77]). PHORA had a specificity of 0.76 [95% CI: 0.69 – 0.84], sensitivity of 0.79 [95% CI: 0.72– 0.82], negative predictive value of 0.30 [95% CI: 0.25 – 0.34] and a positive predictive value of 0.97 [95% CI: 0.96 –0.98] for one-year survival. PHORA demonstrated an AUC of 0.74 and 0.80 when validated in the COMPERA and PHSANZ registry, respectively (e-Figure 2). Importantly, this algorithm is now able to be prepopulated and informed directly by the electronic medical records, so that the probability estimates are available to clinicians as part of their everyday workflow.

5.5. Risk stratification comparison and use in clinical arena

Given the existence of multiple risk tools, it is reasonable to provide data comparing their performance characteristics to inform guideline statements and clinical practice more appropriately. Their relative

performance, whether at baseline or follow-up assessment for predicting 1-year death versus 1-year clinical worsening should be optimized to prevent over and under estimations of risk so that appropriate clinical judgments can be made about adjusting clinical treatment. Ideally, a model used in clinical practice should predict both morbidity and mortality rates with a good discrimination, i.e., C-index > 0.7. In addition, when comparing the relative predictive power of one tool over another, databases using large cohorts of patients not prior used in the development of the tools should be considered.

As noted earlier, our contemporary tools range from poor (C-Index < 0.6) to excellent (C-Index $\geq$ 0.8) discrimination with most falling in the good range (0.7 to 0.8). In addition, compared to baseline assessment, risk stratification tools always perform better at follow-up (consistently in good range) using more contemporaneous data.[59,75,76] Earlier comparisons of tools were hampered by the fact that these comparisons were made in derivation cohorts used to derive or validate each of the individual tools. For example, in the study that developed REVEAL 2.0 model,[34] Benza and colleagues showed that REVEAL 2.0 (used as a continuous score) had the higher C-statistic compared to COMPERA 3-strata and the non-invasive French approach. In the external validation of the COMPERA 4-strata model within the French registry,[76] Boucly *et al* showed that COMPERA 4-strata had a higher C-statistic compared to the 3-strata model both at baseline (0.67 vs 0.63, p < 0.001) and at follow-up (0.73 vs 0.69, p=0.001). Other risk assessment tools were not considered in this study.

Recently, however, several studies have compared the relative performance of existent models in datasets not originally used to develop these tools and two performed statistical evaluations to determine the relevance of numerical differences in C-Indices. In a cohort of 296 patients with PAH, Sahay et al.[308] compared the risk discrimination of REVEAL Lite 2, and the COMPERA 3-strata and 4-strata models at baseline and follow-up. At baseline, the C-statistic of REVEAL Lite 2 was 0.74, compared to 0.63 for the 3-strata model, and 0.68 for the 4-strata model (e-Table 1). The differences in C-statistic between REVEAL Lite 2 and the COMPERA models were statistically significant. At follow-up, REVEAL Lite 2 still exhibited the highest C-statistic (0.74) compared to the 3-strata (0.65) and 4-strata (0.70) models, exhibiting a similar trend to what was seen at baseline (e-Table 2). However, the difference in C-statistic between REVEAL Lite 2 and the 4-strata model was not significant (p=0.10). Importantly, REVEAL 2.0 was not considered in this study. In another analysis, Boucly et al. compared the risk discrimination of REVEAL 2.0, and the European models in 1240 incident patients from the French PAH Registry. In this analysis, the baseline c-index for REVEAL 2.0 was 0.640 (95% CI: 0.611 – 0.669) compared to 0.587 (95% CI: 0.560 – 06.14) for the European 3-strata. At follow-up, the C-indices for the European 4-strata model (0.722 [95% CI: 0.695 – 0.749]) and REVEAL 2.0 (0.718 [95% CI:0.691 – 0.745) were very similar.[287]

Fauvel et al. in a large global harmonized dataset of six contemporary PAH randomized controlled trials with 1425 patients compiled with the assistance of the U.S. FDA, comparisons of the performance (C-Indices) of REVEAL 2.0, REVEAL Lite, European 3-strata, 4-strata and the noninvasive French score were completed. Outcomes analyzed were one-year all-cause mortality at baseline. To compare among the risk assessment tools, 95% Bootstrap confidence intervals (CI) were constructed based on 100 samples from the original dataset, providing a robust method for comparing across the different methods. Then, scatterplots were used to represent head-to-head comparison and pairwise comparison between the 100 samples. Each of the risk tools was able to predict one-year mortality with fair-to-good discrimination capacity. REVEAL 2.0 performed statistically better than the rest of the scores (C-index of 0.73).[26]As previously stated, most of the U.S. analyses reported a statistically significant difference in the C-statistic of the REVEAL models when compared to the European and French approaches, whereas no difference has been demonstrated in a large French multicenter registry.[287] Different analyses have shown differences in C-indices; however, it remains uncertain whether these differences are clinically relevant. Moreover, these findings remain to be validated prospectively. Further analyses comparing outcomes between treatment models based on different risk scores are necessary before making a clear recommendation. Although these risk tools were developed and validated for group 1 PH, their performance in non-group 1 PH requires further validation. A recent multi center analysis may suggest a similar discriminatory capability in this setting. (e-Figure 3, e-Table 3).[300]

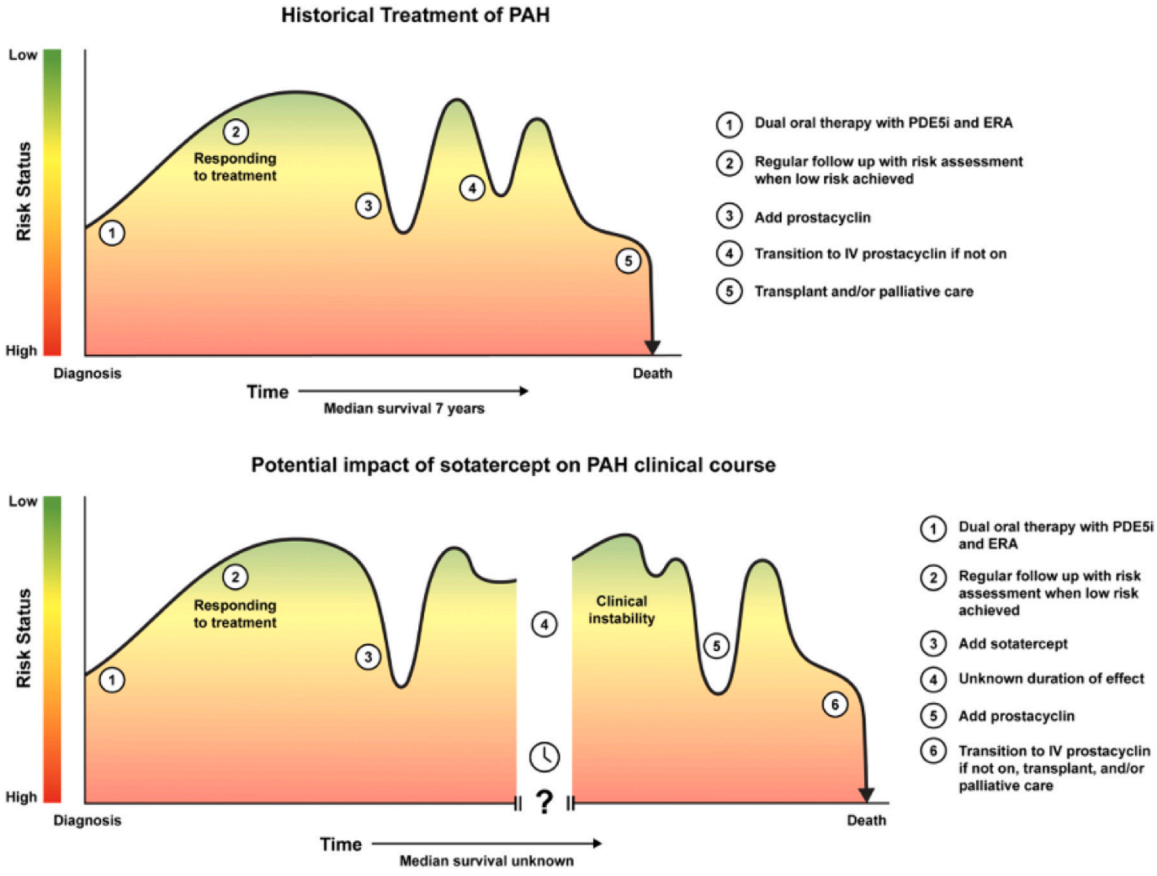
In the clinical arena, guidelines and the 7th WSPH have routinely recommended performing risk stratification.[8] The 2015 ESC/ERS guidelines[7] were the first to recommend use of risk stratification in routine clinical practice. Risk stratification was further revised, and the 2022 ESC/ERS guidelines[6] made treatment recommendations based on the risk status of a patient. Despite guidelines recommendations, the utilization of risk stratification in clinical practice is suboptimal. In a recent survey study of 121 US-based PH clinicians, utilization of risk assessment tools was only 59% (65% of physicians and 48% of non-physicians), with only 19% reporting that they use risk tools routinely.[309] When asked about the barriers that limit the utilization of these risk scores, clinicians offered a variety of reasons ranging from time constraints to the complex nature of the risk tools, and the inability to

integrate them with the electronic medical records. Furthermore, risk tools have been criticized for their retrospective derivation and validation. All the present risk assessments for PAH patients have been derived using traditional statistical methods. The efforts to develop simple risk prediction models have resulted in a lack of robustness with respect to predicting outcome in this complex disease. Also, clinically relevant variables such as rate of disease progression currently remain unaccounted for.

Not surprisingly, only a minority of patients in analysis cohorts during application of risk scores achieved the intended goal of low-risk status at follow-up.[75] There are several possible reasons for this, including the pressing need for better treatments. Another reason is the heterogenous nature of PAH patients that may impact the ability to apply risk scores to every clinical scenario. Such is the case of patients with scleroderma-associated PAH for whom it may be difficult to achieve a low-risk status due to limitations associated with their underlying scleroderma and not necessarily their PAH. On the other hand, younger patients with IPAH may be categorized as low risk despite having marked RV dysfunction that would only be unveiled by imaging or hemodynamics. Hence, the risk scores themselves need to undergo periodic refinements to incorporate new data on predictors of disease progression and mortality and, thereby, maintain their clinical utility. Moreover, as addressed by Ahmed et al., a future emphasis needs to be focused on risk assessment in PAH patients with multiple comorbidities and/or advanced age, where we are likely not able to have the same treatment goals, due to difficulties in reaching the low risk.[310,311]

Recently, Cascino et al. illustrated how risk status evolves over time in patients with PAH, highlighting fluctuations from diagnosis to the time of death or transplant. Even after achieving low-risk status, the progressive nature of PAH leads to regression to higher-risk categories over time, requiring adjustments in therapy. The development and approval of activin signal inhibitors such as sotatercept holds promise for influencing the clinical course and risk trajectories of patients with PAH patients, as shown in Figure 10.[312]

Figure 10 Schema for the hypothetical incorporation and impact of Sotatercept on the management and risk progression of patients with PAH.[312] Reprint permission received from the publisher.



5.6. Enhancements to contemporary risk scores (imaging and hemodynamics)

One of the simplest methods to improve yield of the risk assessment tools is to utilize right ventricular (RV) imaging in combination with the traditional risk assessment tools as current risk assessment tools lack comprehensive assessment of RV. Recent investigations in United States, Italy and the United Kingdom, have demonstrated enhanced discrimination when imaging components[166,185,313] or imaging scores[314] are used as adjuncts to contemporary scoring systems. This, together with the additions of predictive imaging components to the 2022 ERS/ECS risk table may be particularly important to patients who sit on the border zones of risk categories or as a supplement to overall risk assessment in patient considered low or intermediate risk to make sure that overall risk is not underestimated. A classic example is a patient judged to be at low risk by scoring systems, who has continuous and significant derangements in right ventricular or atrial morphology or function.

Recent studies have analyzed the inclusion of echocardiographic parameters to risk stratification tools, such as REVEAL Lite 2, the European 3-strata and the French low risk score with the goal of further improving them. In a retrospective analysis of 111 patients with PAH, Sahay et al.[315] coupled REVEAL Lite 2 scores with different echocardiographic parameters and determined that pairing REVEAL Lite 2 with the LV end diastolic eccentricity index (as a continuous variable) outperformed REVEAL Lite 2 by itself, achieving an AUC of 0.87, compared to 0.77 for REVEAL Lite 2 alone. In a single-center retrospective analysis of 102 PAH patients, a dichotomized value of TAPSE/sPAP (< 0.24 mm/mmHg vs. ≥ 0.24 mm/mmHg) added to the European 3-strata system significantly improved discrimination in the intermediate-risk group, dividing it into an intermediate-to-low-risk and in intermediate-to-high-risk subgroups. Similarly, when added to the FPHN strategy was able to select patients at lower risk among those with 2, 1, and 0 low-risk criteria. Importantly, they concluded that, "adopting functional-hemodynamic echo-derived parameters may provide a more accurate risk stratification in patients with PAH…, particularly in patients at intermediate-risk, that otherwise would have remained less characterized."[316] In a study of 298 incident PAH patients from Germany, a model combining seven variables accurately discriminated 1- and 3-year survival. From the individual traditional model components (ie 6MWD, NYHA FC, natriuretic peptide levels), the addition of TAPSE/sPAP ratio to the approach numerically increased its ability to discriminate outcome status. They concluded that " Real-world data suggest that residual risk can be captured by noninvasive clinical procedures during routine follow-up assessments in patients with PAH and highlights the potential use of echocardiographic imaging to refine risk assessment.[317] In a study of 659 incident PAH patients from 4 independent French PH centers a multivariable Cox regression analysis demonstrated that use of 3 noninvasive low-risk criteria (NYHA functional class), natriuretic peptide levels and TAPSE/sPAP > 0.33 mm/mmHg) accurately predicted 3-year all-cause mortality or need for lung transplantation with a good level of discrimination (c Index > 0.7).[318] A study of 110 Italian PAH patients, the additional use of 4 echo parameters (RVEDA, RA area, and LV eccentricity Index) to the REVEAL 2.0 score provided incremental prognostic power over REVEAL with overall excellent discrimination (C-Index: 0.87, 95% confidence interval [CI]: 0.80 to 0.94, vs. 0.69, 95% CI: 0.58 to 0.79, respectively; p < 0.001).[166]

More recently, El-Kersh et al.[314] developed the REVEAL-ECHO risk score, which involves four echocardiographic parameters (RV enlargement, RV systolic function, tricuspid regurgitation severity, and pericardial effusion), and accounts for PAH etiology. When applied to 2400 adult patients with PAH enrolled in the REVEAL registry, and categorizing patients as low, intermediate, and high risk, statistically significant differences in 12-month mortality was observed. The authors also used this echo-based score to augment REVEAL Lite 2 and reported a separation of REVEAL Lite 2 into a four-strata model (low, intermediate-low, intermediate-high, and high). In another single center study,[315] REVEAL lite 2 was combined with the echocardiographic parameters to predict the risk for the morbid events in addition to mortal events. The AUC for REVEAL lite 2 (0.77) improved significantly (P= 0.04) when combined with LV eccentricity index (0.88). This study highlights that REVEAL lite 2 has potential to perform better when combined with the right ventricular imaging. In fact, a recent Delphi consensus study of the global experts suggested to use RV imaging in decisions of treatment escalation and risk assessment.[319] Right ventricular dimensions and function may also be assessed by simple echocardiographic variables combined to define different phenotypes reflecting progressive severity of maladaptation to failure: RVEDA/LVEDA ≤1 and TAPSE/PASP ≥0.33mm/mmHg (phenotype 1), RVEDA/LVEDA ≤1 and TAPSE/PASP < 0.33mm/mmHg (phenotype 2), RVEDA/LVEDA > 1 and TAPSE/PASP ≥0.33mm/mmHg (phenotype 3) and RVEDA/LVEDA > 1 and TAPSE/PASP < 0.33mm/mmHg, with or without the presence of severe tricuspid regurgitation (respectively, phenotype 4R+ and phenotype 4R-). These RV phenotypes can be observed all across the risk strata, whether considering the ESC/ERS or the REVEAL 2.0 risk scores, and have been associated

with different likelihood of achieving a low-risk status after initial double oral combination (RV phenotype 1, OR 4.0, 95% C.I. 1.6–10.3, p < 0.001; RV phenotype 4 OR 0.28, 95% C.I. 0.16–0.48, p < 0.001), independently of the risk-strata of the patient.[320] Supplemental hemodynamics when added to the European 4-strata systems at follow-up also hold great promise in enhancing risk prediction. Boucly et al.[287] analyzed 1240 incident PAH patients in the French PH network. All patients had hemodynamically confirmed PAH and were diagnosed between 2009–2020. The authors explored whether adding SVO2 or SVI to the European 4-strata system could improve discrimination at first follow-up. They demonstrated that neither of these hemodynamic parameters were associated with transplant free survival among low and high-risk patients by the four-strata. However, in the intermediate-risk group, SVI and SVO2 were found to have prognostic significance. A good hemodynamic profile was defined by at least one criterion among SVI > 37 mL/m^2 and SvO2 > 65% whereas patients having neither SVi > 37 mL/m2, nor SvO2 > 65% had a poor hemodynamic profile. Transplant free survival of patients at intermediate-low risk with good hemodynamic profile was similar at 1 year to that of low-risk patients (97% and 98% respectively) whereas it was worse at 3 years (81% and 91% respectively). Among the intermediate-high risk, hemodynamics identified those with 10% risk of death or transplant in the following year. Statistically, this six strata model (AUC 0.81 [0.76 – 0.86]) performed better than the four strata model (AUC 0.79 [0.74 – 0.84]), and exhibited a higher C-index (0.738 [95% CI: 0.709 – 0.767]) than REVEAL 2.0 (0.718 [95% CI: 0.691 – 0.745]) at follow up.[287]

These recent findings showing the benefit of enhancing our current risk stratification models with imaging and hemodynamic parameters have shown a path forward in risk stratification in PAH. Treatment algorithms have been proposed taking these parameters into consideration. Figure 11 (a and b) provides examples of such algorithms using different risk stratification tools. Figure 11a shows a treatment algorithm by the recent 7th World Symposium on Pulmonary Hypertension (WSPH)[321] and Figure 11b shows an algorithm from a US based perspective developed by Sahay et al.[322] Both algorithms highlight the importance of performing risk status at baseline and each follow up. These examples are being provided to help the clinicians understand how to best utilize any risk method (of their choice) in the treatment decisions.

Key points:

1. Current guidelines and expert consensus recommend that clinicians should perform risk stratification at baseline and follow up evaluation of PAH patients. Recent studies have shown unacceptably low utilization of risk assessment tools in the clinical practice
2. Selection of risk tool to use should be determined by the clinician at bedside depending on the ease, resources, and local practice patterns.
3. Adding novel imaging parameters to contemporary risk scores may improve their predictive ability particularly in the low and intermediate range. Currently, only the European 3-strata model includes imaging parameters, while REVEAL 2.0 includes the presence of pericardial effusion on echocardiogram. Additional validation and selection of the best imaging variables requires further study.
4. Adding novel hemodynamics parameters to contemporary risk calculators at baseline or at first follow-up can improve their predictive power, particularly in the intermediate risk strata; however, its adjunct use may be limited by its invasiveness and availability in a wider community setting.
5. These risk tools need to be prospectively validated in the real-world setting demonstrating the impact of treatment changes based on the risk status on patient outcomes.

5.7. Use of risk stratification in clinical trials

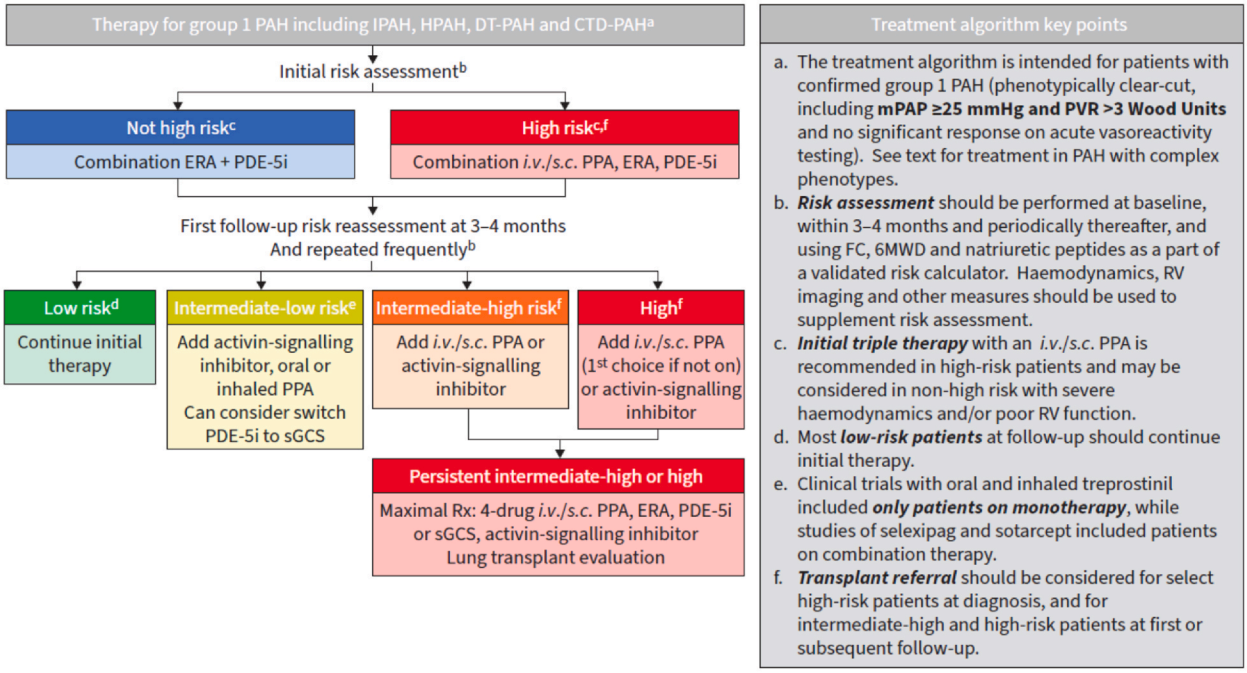
5.7.1. The history of clinical trial end points in PAH

Early therapies for PAH were based on anecdotal evidence, case reports and small case series. In 1990, the first randomized trial of epoprostenol for the treatment of PAH was undertaken.[323] This drug showed improvement in hemodynamics, and exercise capacity (as measured by the 6MWD) over an 8-week period. Whilst positive, this study was very small with only 24 patients. It was not until 1996 that this drug was registered as the first medication for PAH following an additional randomized open label trial.[324] This has been the only trial to date to demonstrate improved survival in PAH, but endpoints again included hemodynamics and 6MWD.

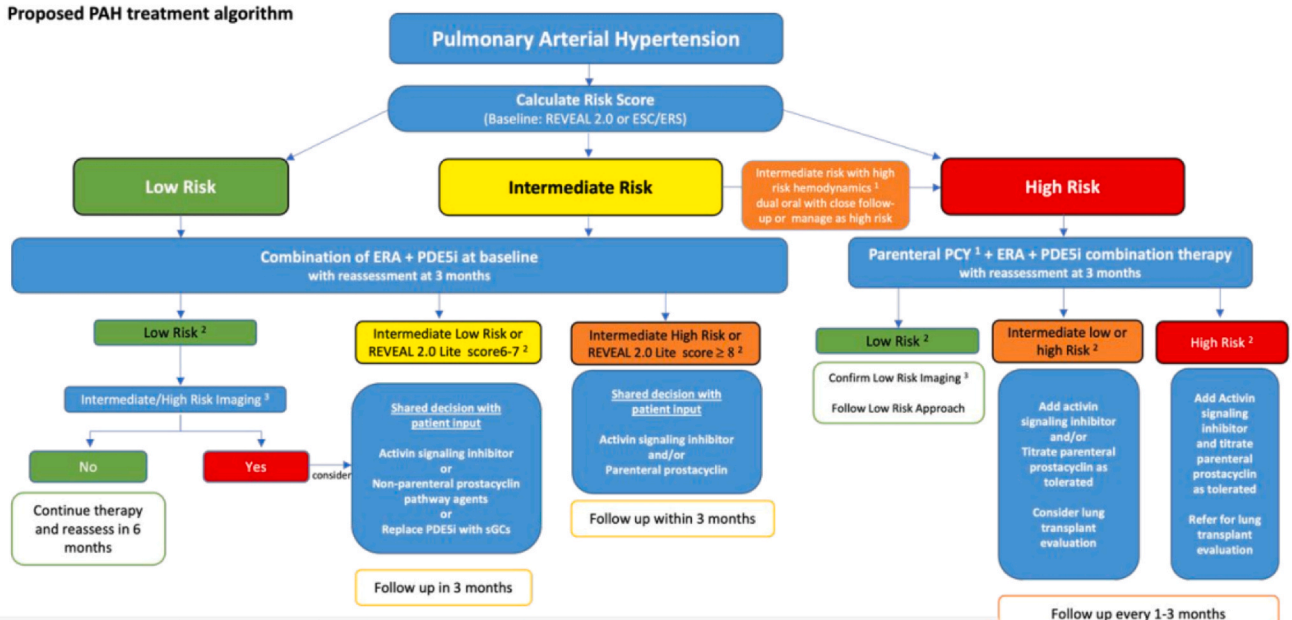
With improved understanding of the pathophysiology of PAH, additional drugs were developed and tested in clinical trials over the next two to three decades. In most of these trials the primary endpoint was change in 6MWD. A short-term improvement in 6MWD was readily accepted by regulatory bodies but has not been shown to clearly

Figure 11 (a &b). Published examples of treatment algorithms using different risk stratification tools.[8,322] Reprint permission received from the publisher.

(a) Treatment algorithm for pulmonary arterial hypertension from the 7th World Symposium on Pulmonary Hypertension



(b) US perspective using REVEAL with ESC/ERS four strata to aid in treatment decisions



** This is a proposed algorithm based on the current evidence and expert opinion where evidence is lacking. It differs from the ESC/ERS guidelines by incorporating sotatercept in the treatment algorithm, REVEAL risk scoring for risk stratification and RV imaging-based approach.

reflect improved outcomes in patients with PAH.[72,325] 6MWD was clearly able to show a difference in monotherapy trials against the placebo arm and continues to be used as a primary endpoint in more recent phase 3 clinical trials (NCT05036135; NCT05934526).[67]

As more drugs for the treatment of PAH become available, the landscape of PAH therapy and clinical trials continues to change and evolve, with patients nowadays being able to receive up to four different PH-specific medications. The access to more therapies, and the achievement of a higher functional capacity raises questions about what endpoints to use in future clinical trials to assess efficacy of novel drugs. From a strictly scientific point of view, mortality benefit is the most desirable and clearly shows the effectiveness of new therapies. Trials using mortality as an endpoint are appropriate when all available treatment options are allowed. A recent clinical trial utilized this endpoint to evaluate the effects of various sildenafil doses on mortality in adults with PAH.[326] On the other hand, conducting mortality trials that prohibit available treatment options is considered controversial as it would delay a potentially lifesaving treatment in a fatal disease such as PAH when there are numerous treatments available to worsening patients. Thus, in recent years clinical trials in PAH have adopted surrogate endpoints that reflect lack of deterioration such as TTCW. This has changed the course of the trials, making them bigger, longer, and significantly more expensive. Moreover, recruitment can be slow in a rare disease such as PAH. Therefore, it is vital to come up with endpoints that properly assess the effectiveness of new drugs, that are clinically relevant to patients, clinicians, and regulators, while also being practical for the recruitment and execution of the clinical trial.

5.7.2. Risk scores as an end point in clinical trials

There have not been any clinical trials that have been designed with a change in risk score as a primary outcome measure.[327] Nevertheless, several authors have utilized clinical trial data to perform *post-hoc* analysis and validate different risk assessment tools, providing some insight into how these models would have performed in each trial (Table 10). In addition, the FREEDOM-EV[328] and the STELLAR[67] trial prospectively specified change in French non-invasive risk score as an exploratory outcome, and the REPLACE trial[329] had a composite improvement (similar to a change in risk) as its primary outcome.

The PATENT-1 clinical trial evaluated the efficacy and side effect profile of riociguat when added to baseline therapy, or as initial therapy versus placebo over 12 weeks in patients with PAH.[330] Data from this trial and its open label extension (PATENT-2)[331] was utilized in a *post-hoc* analysis by Benza et al. to assess the effect of riociguat on REVEAL Lite 2 score. The score was calculated at baseline, week 12, and week 12 of the open label extension (week 24 after randomization for those continuing). A significant improvement (drop) in REVEAL Lite 2 was seen in PATENT-1 patients assigned to the maximal dose of riociguat from baseline to week 12 compared to placebo. Moreover, in PATENT-2, placebo-assigned participants who began riociguat exhibited an improvement in REVEAL Lite 2 at week 12 similar to the one observed in the maximal dose cohort of the main study.[303] Week 12 REVEAL Lite 2 (on therapy or placebo in the blinded phase) predicted event-free survival during the open label phase more accurately than the baseline assessment prior to therapy. In a similar analysis using REVEAL 2.0, a 1-point improvement in RRS 2.0 at PATENT-1 baseline was associated with a 23% reduction in the relative risk of death and a 20% reduction in the relative risk of clinical worsening in PATENT-2. Similarly, a 1-point improvement in RRS 2.0 at PATENT-1 Week 12 was associated with a 26% reduction in the relative risk of death and a 23% reduction in the relative risk of clinical worsening in PATENT-2.[302]

Data from the PATENT-1 trial was also analyzed by Humbert et al.[332] Using three abbreviated versions of the 2015 ESC/ERS risk assessment guidelines,[7] the SPAHR/COMPERA model,[24,60] the French Registry invasive and non-invasive models,[59] risk was assessed at baseline and at the first follow up. Only data from patients who completed PATENT-1 and enrolled in PATENT-2 was included. Six of the variables included in the 2015 ESC/ERS risk stratification table were prospectively collected in PATENT-1 (6MWD, WHO FC, NT-proBNP, RAP, CI and SvO_2). A total of 340 patients are included in the analysis, mostly IPAH (62%), WHO FC III (54%) and approximately 50% were pre-treated with a PAH specific agent. All three assessed methods demonstrated an improvement in risk stratum after 12 weeks of riociguat. Using the French non-invasive and the SPAHR/COMPERA assessments in the riociguat assigned participants, baseline and especially follow-up risk scores predicted event free survival.

GRIPHON was the pivotal randomized controlled trial to assess efficacy and safety of Selexipag.[333] The primary end point was a composite of death or complication related to PAH. In a *post-hoc* analysis of the data obtained in this trial, Sitbon et al. reported that both the number of low-risk criteria achieved per the French non-invasive model and the REVEAL 2.0 risk category were able to predict morbidity and mortality at baseline and at

Table 10 Risk score validation in the clinical trials

Trial Data Set	PATENT 1 & 2[332]	GRIPHON[334]	OPTIMA[335]	FREEDOM-EV[328]	FREEDOM-EV[9]	STELLAR[67]
Risk scoring system(s) used	COMPERA FR invasive FR non-invasive	FR non-invasive REVEAL 2.0	FR invasive FR non-invasive	FR non-invasive	REVEAL 2.0 REVEAL Lite 2 COMPERA 2.0 (4 strata)	FR non-invasive
No. Patients	340 Incident and prevalent	1156 Incident and prevalent	46 Incident	690 Prevalent	690 Prevalent	323 (163 – active drug; 160 – placebo) Prevalent
Treatment Naïve (%)	50	20	100	0	0	0
Etiology of PAH	IPAH, HPAH, A-PAH (CTD, CHD, PoPH)	IPAH, HPAH, A-PAH (CTD, CHD, HIV)	IPAH, HPAH, A-PAH (CTD, CHD, Dr, HIV)	IPAH, HPAH, A-PAH (CTD, CHD, Dr, HIV)	IPAH, HPAH, A-PAH (CTD, CHD, Dr, HIV)	IPAH, HPAH A-PAH (CTD, Drug and toxin, corrected CHD)
Time to 1st follow-up	12 weeks	26 weeks	16 weeks	12 weeks	12 weeks	24 weeks
Analysis	Post hoc	Post hoc	Pre-specified	Pre-specified	Post hoc	Pre-specified
Results	FR invasive tool not discriminatory. FR non-invasive & COMPERA able to predict survival	Both methods able to predict morbidity and mortality.	Changes in the number of low risk criteria correlated with improvement in WHO FC	Risk score able to predict outcome	All scores able to predict outcome with the simpler methods more discriminatory	39.5% of patients who received drug were at low-risk at 24 weeks, compared to 18.2% in the placebo group.

A-PAH, associated PAH; CHD congenital heart disease; COMPERA, comparative prospective registry of newly initiated therapies for pulmonary hypertension; CTD, connective tissue disease; Dr, drugs and toxins induced; FR, French pulmonary hypertension registry; HIV, human immunodeficiency virus; HPAH, heritable PAH; IPAH, idiopathic PAH; PoPH, portopulmonary hypertension; REVEAL, registry to evaluate early and long-term PAH disease management; WHO FC, World Health Organization functional class.

any time point during the study follow-up. Selexipag increased the likelihood of achieving three low risk criteria and a lower REVEAL 2.0 score.[334] In another post-hoc analysis of GRIPHON study changes in REVEAL Lite 2 risk score with selexipag versus placebo, and whether changes were prognostic or predictive of time to first morbidity/mortality (M/M) event were studied. REVEAL Lite 2 risk category discriminated M/M risk (landmark concordance indices: 0.68–0.76, selexipag; 0.65–0.70, placebo). Across baseline risk categories, hazard ratios supported a lower risk of M/M events with selexipag versus placebo: low, 0.573 (95% confidence interval [CI] 0.361–0.908; $p = 0.0178$); intermediate, 0.423 ([0.274–0.655]; $p = 0.0001$); high, 0.711 ([0.520–0.972]; $p = 0.0326$). Odds ratios for risk improvement were 2.0 [1.50–2.65], 1.8 [1.38–2.43], and 2.0 [1.43–2.72] for selexipag versus placebo at 4, 6, and 12 months, respectively (all $p < 0.001$).[307]

OPTIMA was a prospective, multicenter, single arm, open label, phase 4 study that looked at the safety and efficacy of macitentan and tadalafil as up-front combination therapy in treatment naïve, incident patients.[335] The number of low-risk criteria achieved using both the French invasive and non-invasive models were pre-specified exploratory endpoints of the trial. Initial dual oral combination therapy showed improvement in risk scores from baseline to week 16. FREEDOM EV[328] pre-specified the French non-invasive model followed prospectively over time as an exploratory endpoint. Those randomized to oral treprostinil had higher risk scores at baseline and on follow-up more patients had improved risk scores than the placebo group (out to 108 weeks). Those receiving oral treprostinil were also less likely to have worsening risk scores than those receiving placebo.

Benza et al then conducted a post hoc analysis of the FREEDOM EV data and examined the ability of several contemporary risk scores to predict outcomes.[9] The scores used were REVEAL 2.0, REVEAL Lite 2, and COMPERA 2.0 (4 strata). All three of the newer risk scores confirmed the finding from the original publication that the patients randomized to Treprostinil had higher risk scores than those randomized to placebo. All Week 12 scores (on assigned therapy) were better able to predict subsequent clinical worsening (as compared to baseline). The simpler tools like REVEAL Lite 2 and COMPERA 2.0 were more sensitive to improvements in risk and this likely reflects REVEAL 2.0 containing some non-modifiable factors. The authors then conducted a

mediation analysis to determine whether change in risk score accounted for the drug treatment effect on clinical worsening (an analysis for surrogacy as an endpoint). Using all participants, the change in REVEAL Lite 2 risk score (from Baseline to Week 12) accounted for 33% of the treatment effect; when the participants who had low-risk at baseline were excluded, the change in score accounted for 74% of the treatment effect. This data suggested that, especially for participants with intermediate or high-risk at baseline, change in REVEAL Lite 2 score appeared to be a surrogate for clinical worsening. To strengthen this conclusion, the authors reported that only a handful of patients who had achieved French non-invasive low risk status (a composite 'net clinical benefit') at Week 24 had subsequent clinical worsening.[336] In a similar analysis of the GRIPHON data, REVEAL Lite 2 risk improvement at Week 16 explained 19.1% of the treatment effect for all patients and 47% of the treatment effect in patients with a REVEAL Lite 2 baseline of ≥7.[307]

Blette *et al* used patient-level data harmonization strategies to do a mediation analysis on 2508 participants included in the event-driven studies GRIPHON, SERAPHIN, and AMBITION. They concluded that COMPERA low-risk status measured at Week 16 (Week 12 GRIPHON data was interpolated from Weeks 12 and 24) was not a surrogate. Their methodologic approach was substantially different to the FREEDOM-EV authors in that they did not analyze change in risk over time and they dichotomized risk into 'low' and 'not low'; these two factors as well as some features of the participant data (especially a large number of low-risk patients) contributed to their different conclusion.

There is an urgent need to identify therapies which are simultaneously more effective and less burdensome for patients than our current therapies. Time to event trials have taught us much in the field, but they are resource intensive: hundreds of patients commit for years in trials that cost > $300 million. Some intermediate risk participants will languish or deteriorate on placebo to demonstrate efficacy, and those wanting to continue the drug (perhaps with substantial benefit but still needing more therapy) are prevented from participating in other studies while years lapse before approval. Risk scores appear promising as a surrogate that might prove highly discriminatory in 24–48 weeks: reducing costs, time on placebo, and time to approval for treatments which are effective. Longitudinal (every 6–12 weeks) scores over time would probably improve discrimination without increasing cost.[337] Moreover, current risk scores can be used as part of the eligibility criteria for clinical trials to enrich the sample (NCT05934526).

Key points:

1. Risk scores have been shown to predict long term outcomes based on registry data and now in clinical trial data either as post hoc analysis or exploratory endpoints.
2. No trial to date has used any method of assessing risk as the primary endpoint, but the change in risk score seems a worthy candidate for a surrogate of clinical worsening.
3. Simplified scores such as REVEAL Lite 2, the ESC/ERS 4-strata model or the French non-invasive model will likely be more sensitive to therapeutic change as compared to more complex systems that include non-modifiable factors[338].
4. Further refinements in risk scores to improve their predictive value (especially for clinical worsening),[339] and data from trials like HYPERION and ZENITH (NCT04811092 and NCT04896008) which exclude lower risk patients should help.

6. PEDIATRIC PAH RISK ASSESSMENT

Identification of high-risk PH is a key component of disease assessment and treatment. Since the 2015 and 2022 ESC/ERS guidelines for diagnosis and treatment of PH recommended serial risk assessment to guide therapy, numerous studies have demonstrated specific high and low risk features in adult PAH.[6,7] Adult clinical risk assessment for PAH is based on both data derived models, with thresholds for low, medium, and high-risk variables based on large retrospective studies, including external validation studies and expert consensus. Presently, the 2022 ESC/ERS guidelines give a Class I, level of evidence B, recommendation for standardized risk assessment-based therapy.

Risk assessment is also a cornerstone of pediatric PH management. Several prognostic factors have been described in pediatrics. Ploegstra et al (2015) evaluated pediatric prognostic factors in a systematic review identifying FC, NT-proBNP, RAP, indexed PVR, CI, and acute vasodilator response as consistently reported

prognostic markers in different independent cohorts.[340] They further identified specific treatment goals in a longitudinal cohort, showing that improvement in FC, NT-proBNP, and TAPSE predicted transplant free survival in children[341].

Already the 5th and subsequently the 6th World Symposium on PH (2013 and 2018 respectively) and the 2015 AHA/ATS Pediatric Consensus guidelines recommended risk stratification to determine therapy in children; in the absence of pediatric specific risk assessment algorithms, these recommendations support using a preponderance of higher risk factors including higher FC, shorter 6MWD, echocardiographic evidence of RV failure and worse hemodynamic profile.[342,343] The 2019 European Pediatric Pulmonary Vascular Disease Network consensus statement follows these recommendations, but notes these criteria only have a C level of evidence due to sparse data, guidelines based on expert consensus, and studies of individual risk factors in pediatric PAH.[344]

Currently, one study by Haarman et al, in a correspondence in the AJRCCM in 2019, specifically evaluated the use of low and high risk criteria proposed in the WSPH proceedings and EPPVDN guidelines. In 58 children with IPAH/HPAH, a higher number of low risk criteria (including absence of syncope, height and body mass z score > −2, FC I-II, NT-ProBNP < 1200 ng/L, TAPSE > 12 mm, RA area < 18 cm^2, CI > 2.5 L/min/m^2, pulmonary vascular resistance index, ratio of mPAP to mean systemic arterial pressure < 0.75, acute vasodilator response, and SVO2 > 65%) were predictive of better outcome. They further found that an increase in the number of low risk criteria after treatment initiation was predictive of better outcomes.[345] More recently, two systematic reviews of risk assessment (at baseline and serially) by Lokhorst et al. concluded that evidence based risk stratification models in pediatric PH are scarce, but there are some pediatric studies using FC, 6MWD, NT-proBNP, RAP, SVO2 and CI.[346,347] Most importantly, these papers identified the lack of a weighting scheme for any of the included variables in children, lack of pediatric specific variable cutoffs, and lack of prospective validation exist for any pediatric risk model.

Challenges to risk assessment in pediatric PH include limitations of functional assessment such as 6MWT or exercise testing in young children or infants, defining age specific variables that are interpretable across age and size ranges, and the different mixture of comorbidities such as prematurity or genetic abnormalities which are more important for pediatric populations. In the realm of functional assessment, multiple investigative groups have conducted studies to establish normal reference values for 6MWD using healthy children and adolescents over the last 20 years,[348] including a growing number of studies of people of different backgrounds to incorporate various factors including ancestry, diet, and typical degrees of physical activity in a given region. When possible, normative values derived from the population of interest should be used. However, recent systematic reviews have also contributed helpful normative information.[349] Moreover, updated normal values for VO2 max in children, representative of the current pediatric population, have recently been published,[350] although opportunities to determine normal variations according to ethnic background and other features still remain. Equally important, is defining meaningful pediatric functional measures especially in the neonatal and infant populations, both as predictors of risk and as therapeutic goals. Rigorous development and testing of a pediatric risk model is especially important for these patients in whom invasive measures carry higher risk, and functional or subjective assessments are more difficult.

A promising area of research is non-invasive markers of pediatric risk including blood biomarkers, physiologic markers, and non-invasive imaging. Moledina et al identified growth, via z-scored height and weight for age, as predictors of outcomes in pediatric PAH, a measure now reflected in the low-risk criteria for pediatric PAH.[343,344,351] Ploegstra et al characterized growth in a longitudinal study from multiple prospective registries where they demonstrated impaired growth in pediatric PH, particularly associated with congenital heart disease. They further showed the relationship of growth with disease severity and duration but showed that clinical improvement was associated with catch up growth, making height for age a potentially valuable and easy to follow biomarker.[352]

Imaging biomarkers which have been studied in pediatrics include the RV to left ventricular ratio by echocardiogram as a surrogate for the mPAP to mean systemic pressure ratio, RA area, TAPSE, LVEI, fractional area change, and presence of a pericardial effusion.[353,354] In addition, Jone et al have shown a good relationship of the RV:LV end systolic ratio to invasive hemodynamics as well as outcomes. TAPSE has also been well studied with age and size indexed normal values determined and proven to be a useful non-invasive marker of RV function.[355] These imaging variables characterize different aspects of PH pathobiology and risk but could be incorporated into a weighted model of pediatric PH risk.

Blood biomarkers are an interesting tool in pediatric risk prediction because of the ease of collection and objectivity of data. Nonetheless, for a blood biomarker to be successful, it must also be studied across ages, and if

needed, adjusted for age and developmental stage. The most widely described blood biomarkers in pediatric PH are the natriuretic peptides, BNP and NT-proBNP. When increased to high levels they are good predictors of poor outcomes in pediatric PAH, although, as seen in adult studies, they are most informative at high levels. In pediatrics, an NT-proBNP > 1200pg/dL and an increase of > 10% in serial measurements is associated with adverse outcomes.[115,356] There may be differences in NT-proBNP between type of PH, particularly amongst very young or premature infants, infants with lung disease, and children with congenital heart disease.[357] While the natriuretic peptides are commonly used, addition of newer markers may help discriminate amongst patients with intermediate risk. ST2 for example, has been shown in multiple studies to be a good prognostic marker in pediatrics, and is additive to NT-proBNP and other clinical markers further improving risk stratification over NT-proBNP alone.[358] Inflammatory markers, including interleukin 6, growth differentiation factor 15, and galectin 3 have shown some promise but have not been widely studied as risk predictors.[359,360] Uric acid is another promising blood biomarker which is predictive of adverse outcomes both if elevated at baseline, and if increasing over time.[361] Uric acid is easy to measure and widely available, but like many blood biomarkers, it does require adjustment for age, and renal function. In addition to understanding age related effects of blood biomarkers in pediatric PAH, genetic syndromes may also affect levels, and require adjustment; Trisomy 21 for example places children at high risk of PH and may require different growth parameters and cutoffs for blood biomarkers.[362] Blood biomarkers, particularly NT-proBNP, can be informative, objective and easy to measure markers that improve risk discrimination. However, inclusion in a pediatric risk model will still require adjustment for age, developmental variation, possibly using age/size normalized values. Alternatively, many of these markers show good longitudinal performance and could be individualized to each patient as a percent change over time to predict worsening disease.

Genetic syndromes are an extremely important predictor of adverse outcomes in PH and are especially relevant for pediatric PH. Welch and Chung described the significant differences in pediatric versus adult onset disease including the increased burden of genetic factors contributing to pediatric PH, with rare genetic factors contributing to about 42% of pediatric PAH versus 12.5% of adult onset PAH.[363] Zhu et al described BMPR2 mutations in about 70% of adult HPAH; in children however, there was a significantly higher burden of other mutations including substantial contribution of TBX4 mutations as well as other rare deleterious variants such as Caveolin-1, activin A receptor like type 1 (ACVRL1) and endoglin (ENG), and SRY-related HMG-box 17 (Sox-17) in patients with congenital heart disease associated PH.[364,365] Mutations in TBX4 cause a spectrum of pediatric parenchymal lung disease including a severe form of developmental lung disease with early onset, often neonatal, PH.[366,367] In addition to specific deleterious variants, trisomy's are another genetic cause of PH. Trisomy 21, causing Downs syndrome, increases risk for development of multifactorial PH due to a combination of alveolar simplification, airway obstruction, congenital heart disease, and an independent genetic risk.[368] For a pediatric risk score, it would be important to assess the relative contribution of specific variants to outcomes, although it would be challenging to include the spectrum of possible genotypes and phenotypes in a score. A weighted model could be used to give additional importance to certain variants especially with earlier age at diagnosis.

An important feature of the ESC/ERSC risk models are the discrete cutoffs for low versus high-risk variables. These cutoffs are based on adult studies, typically adults in the 5th-7th decades of life and focused on adult WSPH group 1 disease including a high prevalence of IPAH, and CTD. Whether these adult based low and high-risk variables are equally relevant in pediatric patients, particularly those with developmental diseases such as chronic lung disease of prematurity, or congenital heart disease, has not yet been well studied.

By contrast, existing pediatric risk models are focused on IPAH and HPAH, but don't account for the 50% PAH cases in children being due to congenital heart disease associated PH. These patients may have altered hemodynamics due to intracardiac shunts, valvular stenosis or obstruction, and lower systemic and mixed venous saturations. In addition, current pediatric models don't include the significant proportion of children with PH due to developmental lung disease, particularly chronic lung disease of prematurity. Of the 1475 pediatric subjects enrolled in the Pediatric PH Network (PPHNet), 48% have WSPH group 3 PH.[369] Given the variability, hemodynamic and functional measures may need to be considered based on type or subtype. of PH as well as age and developmental factors.

In a study describing hemodynamics in children with PH from the PPHNet registry, the median RAP was 7 mmHg, with a pulmonary vascular resistance index of 5–9 WU. About half of subjects were in FC III-IV, but more than 60% were infants at the time of diagnosis precluding measurement of 6MWD, exercise testing or functional testing.[369] The best predictor of event in this study was the mPAP to mean systemic pressure ratio.[369] Notably, this study included 62% of patients with WSPH group 1 disease and 30% of subjects with WSPH group 3 disease. Conversely, in the TOPP registry, including subject > 3 months of age and RHC-confirmed PH, subjects with PAH

had higher mPAP, and had a pulmonary vascular resistance index of 15–19 WUi whilst those with WSPH group 3 disease had a pulmonary vascular resistance index of 8–11 WUi. WSPH group 3 subjects also had a lower mean pulmonary artery to mean systemic pressure.[352] While these studies are not focused on risk assessment, they provide a broad characterization of hemodynamics in pediatric PH, including the proportion of patients for whom functional variables are not feasible, the significant hemodynamic differences between group 1 and group 3 disease, and the broad age and developmental ranges encountered in pediatric PH. A good pediatric model would need to include both age and development related variable cutoffs but may also include more pediatric relevant variables such as gestational age, and PH type.

There is clearly a need for a well validated pediatric PH risk model. Multiple smaller studies have shown the prognostic value of single or groups of variables including functional, hemodynamic, growth, imaging, and blood biomarkers. Further, many of these have been studied as prognostic factors over time, making them exciting therapeutic targets. Current challenges include developing and validating a risk model in pediatric PH, with pediatric data driven cutoffs for clinical measures. An effective tool will need to consider the variability of ages, effects of growth and development, and differences in phenotype across PH types, particularly between pediatric WSPH group 1 and group 3 disease. This may require multiple scores, variable weighting, or a model that harnesses artificial intelligence or neural network-based models. Lastly, the conduct of clinical trials of existing and emerging therapies for pulmonary hypertension in children is an area of continued focus, with a relative paucity of studies in the pediatric population. Among the challenges include the lack of appropriate clinical trial endpoints and treatment goals. Metrics that specifically improve pediatric risk assessment may prove valuable in this space as novel clinical trial endpoints.[370]

Key points:

1. The use of risk stratification scores has expanded rapidly and has become an integral part of the clinical management of pediatric patients, offering an important tool for the clinician to assess disease severity and response to therapy. This allows adjustment/addition of therapy to achieve and to maintain low risk in these patients.
2. The availability of different risk assessment tools allows a debate over which one should be used and when. However, all systems have some advantages over others and there is no perfect assessment tool yet. Thus, the main thrust should be to ensure some form of risk score is used.
3. It is also clear that some key clinical parameters have been consistently identified across different platforms to be some of the most important and clinically validated at predicting prognosis – 6MWD, WHO-FC, NT-proBNP, and TAPSE. Clearly the advantage of these is that they are routinely available in clinical visits and the integration of these into a multivariable calculation can immediately inform clinical decisions.
4. The development of risk assessment tools that are easy to use at the point of care and include mainly readily clinically available parameters have advanced the field.

7. CONSENSUS STATEMENTS

At least 80% consensus from authors was achieved for the following statements:

1) Current guidelines and expert consensus recommend that clinicians should perform risk stratification at baseline and follow up evaluation of PAH patients.
2) Risk assessment should be used in conjunction with clinical gestalt.
3) Factors associated with worse survival include male sex (particularly over the age of 60), systemic sclerosis-associated PAH, and PAH associated with portal hypertension. Immutable risk factors like age, gender and type of PAH can add predictive value to modifiable factors, especially when using risk prediction for advanced planning.
4) Functional capacity whether subjective (NYHA class) or objective (6MWD, ISWT, ETT, CPET) retains vital predictive value. Choice of objective test depends on local expertise and preference.
5) BNP and NT-proBNP remain the only prognostic biomarkers that are clinically available at this point for prognostication both at baseline and follow up.

6) Imaging of the right ventricle provides significant prognostic information that can help in further refining risk assessments in PAH. Echocardiography is a low-cost and easily accessible test, ideal for serial risk assessment, monitoring disease progression or therapeutic response.
7) Several echocardiographic parameters have been associated with improved prognosis in PAH, and these should be validated in large prospective observational studies or multicenter registries.
8) Traditional hemodynamic parameters like PVR, CO, CI, RAP carry prognostic value at baseline and SVO2, SVI and RAP are prognostic at follow up.
9) Hemodynamic indices that reflect RV function and RV coupling to the pulmonary circulation may be better markers of prognosis and response to therapy than traditional hemodynamic variables but require further multicenter validation studies.
10) The French noninvasive strategy is a simple tool that identifies patients at low risk, especially when all three non-invasive parameters are meet. However, patients who are not categorized as low risk by this method should be reassessed with additional tools to confirm their risk status.
11) Clinicians using the COMPERA risk tools in their clinical practice should follow the 2022 ESC/ERS guidelines and use the comprehensive 3- strata model at baseline, and the 4-strata model at follow-up. For patients in the intermediate low and intermediate high-risk statuses per the 4-strata model, invasive hemodynamics (SVi and SvO2) may be implemented to further refine this model.
12) Clinicians using the US based REVEAL risk tools in their clinical practice should use the REVEAL 2.0 calculator for baseline assessment, and either the REVEAL 2.0 or REVEAL Lite 2 depending on parameters measured for follow up evaluations. REVEAL scoring system should be used as a continuous score.
13) RV imaging can be combined with REVEAL risk tools to improve prognostication by REVEAL risk tools. Further studies are needed in larger registries to validate this.
14) There is a need for a well validated pediatric PH risk model that considers the variability of ages, and the effects of growth and development.
15) Further research is needed to integrate multiple genetic, genomic, and transcriptomic variations into risk model systems.
16) Proteomic discovery using mass spectrometry or other techniques holds promise of identifying new biomarkers that can be added to contemporary risk scores to improve mortality and morbidity risk predictions.
17) Risk scores have the potential to act as surrogate endpoints in clinical trials but need further prospective studies to validate their role. If successful, this would result in reduction in costs, time on placebo, and time to approval for treatments which are effective. Risk scores may also be used for sample enrichment strategies in clinical trials.

DISCLOSURES

No grants or funding were received for this document. SS: Research grants paid to his institution from United Therapeutics, Gossamer Bio, Bayer, Altavant/Enzyvant, Keros, Liquidia, Respira Therapeutics, Merck, Pulmovant. Consulting fees from Janssen, United Therapeutics, Liquidia, Keros, and Merck. Support for attending meetings and/or travel from Janssen. Patent submitted for Janssen as inventor. Advisory board for United Therapeutics, Bayer, Liquidia, Merck, Gossamer. DSMB chair and member for NIH funded trials. Chair of Pulmonary Vascular Disease Section of ACCP CHEST. Member of scientific leadership committee of the Pulmonary Hypertension Association; SV: Consultant for United Therapeutics; ART: participated in advisory panels for Merck and Janssen; NVH: None; EDA: Member of the Scientific Advisory Board for Merck, Inc. (unpaid). Grants from the NIH and a leadership role with TBX4Life; RB: Personal fees from UT, Dompè, Ferrer, Bayer, MSD and AOP Orphan Pharmaceuticals; RMFB: Grants from Johnson & Johnson, consultancy fees from Johnson & Johnson, GSK and Ferrer, payment for educational events from Johnson & Johnson, Ferrer, AOP, MSD, Heart Medical, Occlutech Salveo, Bayer and Gossamerbio, participation on a data safety monitoring board or advisory board with MSD, and leadership roles with TOPP-registry, PPHNet and the ESC/ERS 2022 guidelines for diagnosis and treatment of pulmonary hypertension task force; AB: Supported by ERS/EU RESPIRE4 Marie Skłodowska-Curie Postdoctoral Research Fellowship (R4202205–00947), and reports grants from Acceleron, Janssen, and MSD, payment or honoraria for lectures, presentations, manuscript writing, or educational events from Janssen, Merck, AOP Orphan, Ferrer, and AstraZeneca, and support for attending meetings from Janssen, MSD, Ferrer, and AOP

Orphan; YC: None; CC: None; MD: Research grants from Actelion Pharmaceuticals US, Inc., (a Johnson & Johnson Company); and speaker and consultant fees from Bayer, MSD, Acceleron, AOP Health, Daiichi Sankyo. Holder of the Janssen Chair for Pulmonary Hypertension at the KU Leuven; ADE: Consulting fees from Merck; HWF: Scientific Advisoty Boards for Actelion (Janssen), Acceleron (Merck), Aerovate, Aerami, Roivant and United Therapeutics. Speaker for Bayer. Adjudicator for Keros; CF: None; MGM: Research grants paid to her institution from Aerovate, Altavant, Acceleron (a subsidiary of Merck), and Bayer. Consultation fees from Aerami, Acceleron (a subsidiary of Merck), Apollo Therapeutics, Bayer, Janssen Biotech, Jucabio, Keros Therapeutics, Respira Therapeutics and United Therapeutics Corporation. Leadership roles on the Board of Directors for the International Society of Heart and Lung Transplantation and the Scientific Advisory Board of United Therapeutics. Her spouse is a Senior Director in Clinical Development at Intellia Therapeutics; FH: Research funding for investigator-initiated study by Janssen on computational approaches to surrogate end-point research in pulmonary hypertension; YH: None; AH: Research grants from NIH/NHLBI. Consultation fees from Gossamer Bio, United Therapeutics, Merck, Janssen; MHH: Consulting fees from Acceleron, Actelion, AOP Health, Bayer, Ferrer, Gossamer Bio, Inhibikase, Janssen, Keros, MSD, Novartis. Payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events from Actelion, AOP Health, Bayer, Ferrer, Janssen, MSD; MKK: None; DL: Consulting or advisory and speaking and lecture fees from United Therapeutics; SM: None; KMO: Consultant or speaker for Acceleron, Actelion, AOP Orphan, Bayer Healthcare, Ferrer, Gossamer Bio, Janssen Global Services, and Merck; IP: Research grants paid to her institution by United Therapeutics, Merck, Keros, Janssen. Consulting fees from United Therapeutics, Respira Therapeutics, Merck, Liquidia, Keros, Janssen, Insmed, Gossamer Bio. Advisory Board member for Aerovate, Altavant. Steering Committee member for Acceleron. DMC Chair for Tectonic Therapeutic; GR: Research grants paid to his institution from Acceleron, Actelion, Bayer, GlaxoSmithLkine, Janssen, Merck, Pfizer, United Therapeutics, Novartis. Consulting or advisory for Actelion, Bayer, GlaxoSmithKline, Janssen, Nordic Infucare; OS: Research grants paid to his institution from Aerovate, AOP Orphan, Ferrer, Janssen, Merck. Consulting fees from Altavant/Enzyvant, AOP Orphan, Ferrer, Gossamer Bio, Janssen, Liquidia, Merck, Respira Therapeutics, Roivant Sciences, United Therapeutics. Payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events from Aerovate, AOP Orphan, Janssen, Ferrer, Merck. Participation on a Data Safety Monitoring Board or Advisory Board for Altavant/Enzymant, Gossamer Bio, Janssen, Respira Therapeutics; MGT: None; JLV: Consulting fees from Gossamer Bio, Liquidia, Pulmovant, Keros, Johnson & Johnson, Merck; RV: None; JW: Research grants paid to his institution from Janssen, 35Pharma, Merck, Astra Zeneca, Sanofi. Consulting fees from Janssen, Merck, Apollo. Payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or education events from Janssen, Merck. Payment for expert testimony from Sprigings Intellectual Property Law. Support for attending meetings and/or travel from Janssen, Merck. Participation on a Data Safety Monitoring Board or Advisory Board from Janssen, Merck, Universite Laval, Cambridge University. Leadership roles in Pulmonary Hypertension Association of Canada and Pulmonary Vascular Research Institute; RJW: Research grants paid to his institution from United Therapeutics, Merck, Gossamer, Liquidia. Consulting fees from Merck. Support for attending meetings and/or travel from United Therapeutics; HW: None; MW: Consulting fees from United Therapeutics, Actelion, Bayer, Janssen. Speaking fees from United Therapeutics, Actelion, Bayer. Travel reimbursement from United Therapeutics and Actelion; RB: Research grants paid to his institution from Actelion, Bayer, Bellerophon Therapeutics, and Eiger Biopharmaceuticals. Consulting fees from Abbott, Bayer, United Therapeutics. Figure is reproduced with permission from the publisher.

ACKNOWLEDGMENTS

Abdulla Ahmed, MD, PhD student; Salaheldin Ahmed, MD, PhD student; David Kylhammar, MD, PhD, with respect to update and initial development of the SPAHR risk stratification model.

We acknowledge support from Ms Joanne Park MFA and Rachael Whitehead MS, from the graphic designing office of Houston Methodist Research Institute for development of figures for this manuscript. Graphical abstract was created using pictures from Servier Medical Art, by Servier (http://smart.servier.com).

Pulmonary Hypertension Program at Houston Methodist Hospital is supported by the Charles Chapman Philanthropic Pulmonary Hypertension grant.

References

1. Kovacs G, Bartolome S, Denton CP, et al. Definition, classification and diagnosis of pulmonary hypertension. Eur Respir J 2024.
2. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013;62(25):D42-50.
3. Hoeper MM, Humbert M, Souza R, et al. A global view of pulmonary hypertension. Lancet Respir Med 2016;4(4):306-22.
4. Maron BA, Bortman G, De Marco T, et al. Pulmonary hypertension associated with left heart disease. Eur Respir J 2024.
5. Shlobin OA, Adir Y, Barbera JA, et al. Pulmonary hypertension associated with lung diseases. Eur Respir J 2024.
6. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2023;61(1).
7. Galie N, Humbert M, Vachiery JL, et al. 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 (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37(1):67-119.
8. Dardi F, Boucly A, Benza R, et al. Risk stratification and treatment goals in pulmonary arterial hypertension. Eur Respir J 2024.
9. Benza RL, Gomberg-Maitland M, Farber HW, et al. Contemporary risk scores predict clinical worsening in pulmonary arterial hypertension - An analysis of FREEDOM-EV. J Heart Lung Transpl 2022;41(11):1572-80.
10. Thenappan T, Shah SJ, Rich S, Gomberg-Maitland M. A USA-based registry for pulmonary arterial hypertension: 1982 2006. Eur Respir J 2007;30(6):1103-10.
11. Thenappan T, Shah SJ, Rich S, Tian L, Archer SL, Gomberg-Maitland M. Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. Eur Respir J 2010;35(5):1079-87.
12. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010;122(2):164-72.
13. Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL risk score calculator in newly diagnosed patients with pulmonary arterial hypertension. Chest 2011.
14. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from REVEAL. Chest 2012.
15. Benza RL, Miller DP, Foreman AJ, et al. Prognostic implications of serial risk score assessments in patients with pulmonary arterial hypertension: a registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL) analysis. J Heart Lung Transpl 2015;34(3):356-61.
16. Benza RL, Gomberg-Maitland M, Elliott CG, et al. 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 2019.
17. Benza RL, Kanwar MK, Raina A, et al. Development and validation of an abridged version of the REVEAL 2.0 risk score calculator, REVEAL Lite 2, for use in patients with pulmonary arterial hypertension. Chest 2020.
18. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006;173(9):1023-30.
19. Humbert M, Sitbon O, Chaouat A, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation 2010;122(2):156-63.
20. Humbert M, Sitbon O, Yaici A, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. Eur Respir J 2010;36(3):549-55.
21. Lee WT, Ling Y, Sheares KK, Pepke-Zaba J, Peacock AJ, Johnson MK. Predicting survival in pulmonary arterial hypertension in the UK. Eur Respir J 2012;40(3):604-11.
22. Hoeper MM, Huscher D, Ghofrani HA, et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. Int J Cardiol 2012.
23. Radegran G, Kjellstrom B, Ekmehag B, et al. Characteristics and survival of adult Swedish PAH and CTEPH patients 2000-2014. Scand Cardiovasc J 2016;50(4):243-50.

24. Kylhammar D, Kjellstrom B, Hjalmarsson C, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. Eur Heart J 2018;39(47):4175-81.

25. Ahmed A, Ahmed S, Kempe D, Radegran G. Evaluation of the European Society of Cardiology/European Respiratory Society derived three- and four-strata risk stratification models in pulmonary arterial hypertension: introducing an internet-based risk stratification calculator. Eur Heart J Open 2023;3(2):oead012.

26. Fauvel C, Lin S, Correa-Jaque P, et al. Abstract 16736: comparison of pulmonary arterial hypertension risk assessment tools using a harmonized FDA dataset. Circulation 2023;148(_1). A16736-A.

27. Hemnes AR, Beck GJ, Newman JH, et al. PVDOMICS: a multi-center study to improve understanding of pulmonary vascular disease through phenomics. Circ Res 2017;121(10):1136-9.

28. Majeed RW, Wilkins MR, Howard L, et al. Pulmonary Vascular Research Institute GoDeep: a meta-registry merging deep phenotyping datafrom international PH reference centers. Pulm Circ 2022;12(3):e12123.

29. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987;107(2):216-23.

30. Lau EMT, Giannoulatou E, Celermajer DS, Humbert M. Epidemiology and treatment of pulmonary arterial hypertension. Nat Rev Cardiol 2017;14(10):603-14.

31. Hoeper MM, Huscher D, Ghofrani HA, et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. Int J Cardiol 2013;168(2):871-80.

32. Escribano-Subias P, Blanco I, Lopez-Meseguer M, et al. Survival in pulmonary hypertension in Spain: insights from the Spanish registry. Eur Respir J 2012;40(3):596-603.

33. Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. Chest 2012;141(2):354-62.

34. Benza RL, Gomberg-Maitland M, Elliott CG, et al. 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 2019;156(2):323-37.

35. Condliffe R, Kiely DG, Peacock AJ, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. Am J Respir Crit Care Med 2009;179(2):151-7.

36. Chung L, Farber HW, Benza R, et al. Unique predictors of mortality in patients with pulmonary arterial hypertension associated with systemic sclerosis in the REVEAL registry. Chest 2014;146(6):1494-504.

37. Rubenfire M, Huffman MD, Krishnan S, Seibold JR, Schiopu E, McLaughlin VV. Survival in systemic sclerosis with pulmonary arterial hypertension has not improved in the modern era. Chest 2013;144(4):1282-90.

38. Launay D, Sitbon O, Le Pavec J, et al. Long-term outcome of systemic sclerosis-associated pulmonary arterial hypertension treated with bosentan as first-line monotherapy followed or not by the addition of prostanoids or sildenafil. Rheumatol (Oxf) 2010;49(3):490-500.

39. Mathai SC, Hassoun PM. Pulmonary arterial hypertension in connective tissue diseases. Heart Fail Clin 2012;8(3):413-25.

40. Fisher MR, Mathai SC, Champion HC, et al. Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. Arthritis Rheum 2006;54(9):3043-50.

41. Lefevre G, Dauchet L, Hachulla E, et al. Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: a systematic review and meta-analysis. Arthritis Rheum 2013;65(9):2412-23.

42. Abdul-Salam VB, Wharton J, Cupitt J, Berryman M, Edwards RJ, Wilkins MR. Proteomic analysis of lung tissues from patients with pulmonary arterial hypertension. Circulation 2010;122(20):2058-67.

43. Le Pavec J, Souza R, Herve P, et al. Portopulmonary hypertension: survival and prognostic factors. Am J Respir Crit Care Med 2008;178(6):637-43.

44. Sithamparanathan S, Nair A, Thirugnanasothy L, et al. Survival in portopulmonary hypertension: outcomes of the United Kingdom National Pulmonary Arterial Hypertension Registry. J Heart Lung Transpl 2017;36(7):770-9.

45. Krowka MJ, Miller DP, Barst RJ, et al. Portopulmonary hypertension: a report from the US-based REVEAL Registry. Chest 2012;141(4):906-15.

46. Opravil M, Pechere M, Speich R, et al. HIV-associated primary pulmonary hypertension. a case control study. Swiss HIV Cohort Study. Am J Respir Crit Care Med 1997;155(3):990-5.

47. Nunes H, Humbert M, Sitbon O, et al. Prognostic factors for survival in human immunodeficiency virus-associated pulmonary arterial hypertension. Am J Respir Crit Care Med 2003;167(10):1433-9.

48. Rajaratnam A, Rehman S, Sharma P, et al. Right ventricular load and contractility in HIV-associated pulmonary hypertension. PLoS One 2021;16(2):e0243274.

49. Petitpretz P, Brenot F, Azarian R, et al. Pulmonary hypertension in patients with human immunodeficiency virus infection. Comparison with primary pulmonary hypertension. Circulation 1994;89(6):2722-7.

50. van Loon RL, Roofthooft MT, Hillege HL, et al. Pediatric pulmonary hypertension in the Netherlands: epidemiology and characterization during the period 1991 to 2005. Circulation 2011;124(16):1755-64.

51. Verheugt CL, Uiterwaal CS, van der Velde ET, et al. Mortality in adult congenital heart disease. Eur Heart J 2010;31(10):1220-9.

52. Barst RJ, Ivy DD, Foreman AJ, McGoon MD, Rosenzweig EB. Four- and seven-year outcomes of patients with congenital heart disease-associated pulmonary arterial hypertension (from the REVEAL Registry). Am J Cardiol 2014;113(1):147-55.

53. Kempny A, Hjortshoj CS, Gu H, et al. Predictors of death in contemporary adult patients with eisenmenger syndrome: a multicenter study. Circulation 2017;135(15):1432-40.

54. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galie N. Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. Eur Heart J 2014;35(11):716-24.

55. Ploegstra MJ, Ivy DD, Beghetti M, et al. Long-term outcome of children with newly diagnosed pulmonary arterial hypertension: results from the global TOPP registry. Eur Heart J Qual Care Clin Outcomes 2024;10(1):66-76.

56. Rich S. Primary pulmonary hypertension: executive summary from the World Symposium on Primary Pulmonary Hypertension 1998. Evian, France: World Health Organization,; 1999:1-30.

57. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002;40(4):780-8.

58. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002;106(12):1477-82.

59. Boucly A, Weatherald J, Savale L, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. Eur Respir J 2017;50(2).

60. Hoeper MM, Kramer T, Pan Z, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur Respir J 2017;50(2).

61. Barst RJ, Chung L, Zamanian RT, Turner M, McGoon MD. Functional class improvement and 3-year survival outcomes in patients with pulmonary arterial hypertension in the REVEAL Registry. Chest 2013;144(1):160-8.

62. Nickel N, Golpon H, Greer M, et al. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. Eur Respir J 2012;39(3):589-96.

63. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005;353(20):2148-57.

64. Galie N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. Circulation 2009;119(22):2894-903.

65. Galie N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation 2008;117(23):3010-9.

66. Tapson VF, Gomberg-Maitland M, McLaughlin VV, et al. Safety and efficacy of IV treprostinil for pulmonary arterial hypertension: a prospective, multicenter, open-label, 12-week trial. Chest 2006;129(3):683-8.

67. Hoeper MM, Badesch DB, Ghofrani HA, et al. Phase 3 trial of sotatercept for treatment of pulmonary arterial hypertension. N Engl J Med 2023;388(16):1478-90.

68. Halliday SJ, Wang L, Yu C, et al. Six-minute walk distance in healthy young adults. Respir Med 2020;165:105933.

69. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. Eur Respir J 1999;14(2):270-4.

70. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med 1998;158(5 Pt 1):1384-7.

71. Hoeper MM, Pausch C, Olsson KM, et al. Prognostic value of improvement endpoints in pulmonary arterial hypertension trials: a COMPERA analysis. J Heart Lung Transpl 2022;41(7):971-81.

72. Savarese G, Paolillo S, Costanzo P, et al. 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 2012;60(13):1192-201.

73. 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 Transpl 2015;34(3):362-8.

74. Zelniker TA, Huscher D, Vonk-Noordegraaf A, et al. The 6MWT as a prognostic tool in pulmonary arterial hypertension: results from the COMPERA registry. Clin Res Cardiol 2018;107(6):460-70.

75. Hoeper MM, Pausch C, Olsson KM, et al. COMPERA 2.0: a refined four-stratum risk assessment model for pulmonary arterial hypertension. Eur Respir J 2022;60(1).

76. Boucly A, Weatherald J, Savale L, et al. External validation of a refined four-stratum risk assessment score from the French pulmonary hypertension registry. Eur Respir J 2022;59(6).

77. Moutchia J, McClelland RL, Al-Naamani N, et al. Minimal clinically important difference in the 6-minute-walk distance for patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 2023;207(8):1070-9.

78. Lachant DJ, Light AN, Mackin ML, Schwartz RG, White RJ. Heart rate expenditure correlates with right ventricular function. Ann Am Thorac Soc 2020;17(3):372-5.

79. Lachant DJ, Light A, Offen M, Adams J, White RJ. Heart rate monitoring improves clinical assessment during 6-min walk. Pulm Circ 2020;10(4). 2045894020972572.

80. Lachant D, Kennedy E, Derenze B, Light A, Lachant M, White RJ. Cardiac effort to compare clinic and remote 6-minute walk testing in pulmonary arterial hypertension. Chest 2022;162(6):1340-8.

81. Lewis RA, Billings CG, Hurdman JA, et al. Maximal exercise testing using the incremental shuttle walking test can be used to risk-stratify patients with pulmonary arterial hypertension. Ann Am Thorac Soc 2021;18(1):34-43.

82. Laveneziana P, Di Paolo M, Palange P. The clinical value of cardiopulmonary exercise testing in the modern era. Eur Respir Rev 2021;30(159).

83. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation 2001;104(4):429-35.

84. Mancini D, LeJemtel T, Aaronson K. Peak VO(2): a simple yet enduring standard. Circulation 2000;101(10):1080-2.

85. Wensel R, Francis DP, Meyer FJ, et al. Incremental prognostic value of cardiopulmonary exercise testing and resting haemodynamics in pulmonary arterial hypertension. Int J Cardiol 2013;167(4):1193-8.

86. Wensel R, Opitz CF, Anker SD, et al. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. Circulation 2002;106(3):319-24.

87. Deboeck G, Scoditti C, Huez S, et al. Exercise testing to predict outcome in idiopathic versus associated pulmonary arterial hypertension. Eur Respir J 2012;40(6):1410-9.

88. Badagliacca R, Rischard F, Giudice FL, et al. Incremental value of cardiopulmonary exercise testing in intermediate-risk pulmonary arterial hypertension. J Heart Lung Transpl 2022;41(6):780-90.

89. Badagliacca R, Papa S, Poscia R, et al. The added value of cardiopulmonary exercise testing in the follow-up of pulmonary arterial hypertension. J Heart Lung Transpl 2019;38(3):306-14.

90. Wensel R, Opitz C, Anker S, et al. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. Circulation 2002;106:319-24.

91. Groepenhoff H, Vonk-Noordegraaf A, Boonstra A, Spreeuwenberg MD, Postmus PE, Bogaard HJ. Exercise testing to estimate survival in pulmonary hypertension. Med Sci Sports Exerc 2008;40(10):1725-32.

92. McLaughlin VV, Gaine SP, Howard LS, et al. Treatment goals of pulmonary hypertension. J Am Coll Cardiol 2013;62(25):D73-81.

93. Oudiz RJ, Midde R, Hovenesyan A, et al. Usefulness of right-to-left shunting and poor exercise gas exchange for predicting prognosis in patients with pulmonary arterial hypertension. Am J Cardiol 2010;105(8):1186-91.

94. Amedro P, Guillaumont S, Bredy C, Matecki S, Gavotto A. Atrial septal defect and exercise capacity: value of cardio-pulmonary exercise test in assessment and follow-up. J Thorac Dis 2018;10(24):S2864-73.

95. Oudiz RJ, Barst RJ, Hansen JE, et al. Cardiopulmonary exercise testing and six-minute walk correlations in pulmonary arterial hypertension. Am J Cardiol 2006;97(1):123-6.

96. Frost A, Badesch D, Gibbs JSR, et al. Diagnosis of pulmonary hypertension. Eur Respir J 2019;53(1).

97. Dumitrescu D, Nagel C, Kovacs G, et al. Cardiopulmonary exercise testing for detecting pulmonary arterial hypertension in systemic sclerosis. Heart 2017;103(10):774-82.

98. Gomberg-Maitland M, Huo D, Benza RL, McLaughlin VV, Tapson VF, Barst RJ. Creation of a model comparing 6-minute walk test to metabolic equivalent in evaluating treatment effects in pulmonary arterial hypertension. J Heart Lung Transpl 2007;26(7):732-8.

99. Patterson JA, Naughton J, Pietras RJ, Gunnar RM. Treadmill exercise in assessment of the functional capacity of patients with cardiac disease. Am J Cardiol 1972;30(7):757-62.

100. Shah SJ, Thenappan T, Rich S, Sur J, Archer SL, Gomberg-Maitland M. Value of exercise treadmill testing in the risk stratification of patients with pulmonary hypertension. Circ Heart Fail 2009;2(4):278-86.

101. Hsu CH, Glassner C, Foreman AJ, et al. Treadmill testing improves survival prediction models in pulmonary arterial hypertension. Am Heart J 2011;162(6):1011-7.

102. Howard LS, Rosenkranz S, Frantz RP, et al. Assessing daily life physical activity by actigraphy in pulmonary arterial hypertension: insights from the randomized controlled study with selexipag (TRACE). Chest 2023;163(2):407-18.

103. Lachant D, Light A, Lachant M, et al. Peak steps: capacity for activity improves after adding approved therapy in pulmonary arterial hypertension. Pulm Circ 2023;13(3):e12285.

104. Hemnes AR, Silverman-Lloyd LG, Huang S, et al. A mobile health intervention to increase physical activity in pulmonary arterial hypertension. Chest 2021;160(3):1042-52.

105. Smits AJ, Botros L, Mol MAE, et al. A systematic review with meta-analysis of biomarkers for detection of pulmonary arterial hypertension. ERJ Open Res 2022;8(2).

106. Banaszkiewicz M, Gasecka A, Darocha S, et al. Circulating blood-based biomarkers in pulmonary hypertension. J Clin Med 2022;11(2).

107. Semenov AG, Katrukha AG. Analytical issues with natriuretic peptides - has this been overly simplified? EJIFCC 2016;27(3):189-207.

108. Lainchbury JG, Campbell E, Frampton CM, Yandle TG, Nicholls MG, Richards AM. Brain natriuretic peptide and n-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. J Am Coll Cardiol 2003;42(4):728-35.

109. Lewis RA, Durrington C, Condliffe R, Kiely DG. BNP/NT-proBNP in pulmonary arterial hypertension: time for point-of-care testing? Eur Respir Rev 2020;29(156).

110. Frantz RP, Farber HW, Badesch DB, et al. Baseline and serial brain natriuretic peptide level predicts 5-year overall survival in patients with pulmonary arterial hypertension: data from the REVEAL registry. Chest 2018;154(1):126-35.

111. Nagaya N, Nishikimi T, Uematsu M, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation 2000;102(8):865-70.

112. Williams MH, Handler CE, Akram R, et al. Role of N-terminal brain natriuretic peptide (N-TproBNP) in scleroderma-associated pulmonary arterial hypertension. Eur Heart J 2006;27(12):1485-94.

113. Al-Naamani N, Palevsky HI, Lederer DJ, et al. Prognostic significance of biomarkers in pulmonary arterial hypertension. Ann Am Thorac Soc 2016;13(1):25-30.

114. Hendriks PM, van de Groep LD, Veen KM, et al. Prognostic value of brain natriuretic peptides in patients with pulmonary arterial hypertension: a systematic review and meta-analysis. Am Heart J 2022;250:34-44.

115. Mauritz GJ, Rizopoulos D, Groepenhoff H, et al. Usefulness of serial N-terminal pro-B-type natriuretic peptide measurements for determining prognosis in patients with pulmonary arterial hypertension. Am J Cardiol 2011;108(11):1645-50.

116. Chin KM, Rubin LJ, Channick R, et al. Association of N-terminal pro brain natriuretic peptide and long-term outcome in patients with pulmonary arterial hypertension. Circulation 2019;139(21):2440-50.

117. Benza RL, Kanwar MK, Raina A, et al. Development and validation of an abridged version of the REVEAL 2.0 risk score calculator, REVEAL Lite 2, for use in patients with pulmonary arterial hypertension. Chest 2021;159(1):337-46.

118. Jafri L, Kashif W, Tai J, et al. B-type natriuretic peptide versus amino terminal pro-B type natriuretic peptide: selecting the optimal heart failure marker in patients with impaired kidney function. BMC Nephrol 2013;14:117.

119. Fu S, Ping P, Wang F, Luo L. Synthesis, secretion, function, metabolism and application of natriuretic peptides in heart failure. J Biol Eng 2018;12:2.

120. Wang TJ, Larson MG, Levy D, et al. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. Am J Cardiol 2002;90(3):254-8.

121. Raymond I, Groenning BA, Hildebrandt PR, et al. The influence of age, sex and other variables on the plasma level of N-terminal pro brain natriuretic peptide in a large sample of the general population. Heart 2003;89(7):745-51.

122. Wang TJ, Larson MG, Levy D, et al. Impact of obesity on plasma natriuretic peptide levels. Circulation 2004;109(5):594-600.

123. Mehra MR, Uber PA, Park MH, et al. Obesity and suppressed B-type natriuretic peptide levels in heart failure. J Am Coll Cardiol 2004;43(9):1590-5.

124. Clerico A, Carlo Zucchelli G, Pilo A, Passino C, Emdin M. Clinical relevance of biological variation: the lesson of brain natriuretic peptide (BNP) and NT-proBNP assay. Clin Chem Lab Med 2006;44(4):366-78.

125. Torres G, Yang J, Griffiths M, et al. Insulin-like growth factor binding Protein-4: a novel indicator of pulmonary arterial hypertension severity and survival. Pulm Circ 2023;13(2):e12235.

126. Simpson CE, Damico RL, Hassoun PM, et al. Noninvasive prognostic biomarkers for left-sided heart failure as predictors of survival in pulmonary arterial hypertension. Chest 2020;157(6):1606-16.

127. Boucly A, Tu L, Guignabert C, et al. Cytokines as prognostic biomarkers in pulmonary arterial hypertension. Eur Respir J 2023;61(3).

128. Guignabert C, Savale L, Boucly A, et al. Serum and pulmonary expression profiles of the activin signaling system in pulmonary arterial hypertension. Circulation 2023;147(24):1809-22.

129. Qin X, Li T, Sun W, Guo X, Fang Q. Proteomic analysis of pulmonary arterial hypertension. Ther Adv Chronic Dis 2021;12. 20406223211047304.

130. Zhang J, Zhang Y, Li N, et al. Potential diagnostic biomarkers in serum of idiopathic pulmonary arterial hypertension. Respir Med 2009;103(12):1801-6.

131. Yuan C, Chen HX, Hou HT, Wang J, Yang Q, He GW. Protein biomarkers and risk scores in pulmonary arterial hypertension associated with ventricular septal defect: integration of multi-omics and validation. Am J Physiol Lung Cell Mol Physiol 2020;319(5):L810-22.

132. Nies MK, Yang J, Griffiths M, et al. Proteomics discovery of pulmonary hypertension biomarkers: Insulin-like growth factor binding proteins are associated with disease severity. Pulm Circ 2022;12(2):e12039.

133. Xu W, Comhair SAA, Chen R, et al. Integrative proteomics and phosphoproteomics in pulmonary arterial hypertension. Sci Rep 2019;9(1):18623.

134. Rice LM, Mantero JC, Stratton EA, et al. Serum biomarker for diagnostic evaluation of pulmonary arterial hypertension in systemic sclerosis. Arthritis Res Ther 2018;20(1):185.

135. Rhodes CJ, Wharton J, Ghataorhe P, et al. Plasma proteome analysis in patients with pulmonary arterial hypertension: an observational cohort study. Lancet Respir Med 2017;5(9):717-26.

136. Rhodes CJ, Wharton J, Swietlik EM, et al. Using the plasma proteome for risk stratifying patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 2022;205(9):1102-11.

137. Sweatt AJ, Miyagawa K, Rhodes CJ, et al. Severe pulmonary arterial hypertension is characterized by increased neutrophil elastase and relative elafin deficiency. Chest 2021;160(4):1442-58.

138. Koudstaal T, van Uden D, van Hulst JAC, et al. Plasma markers in pulmonary hypertension subgroups correlate with patient survival. Respir Res 2021;22(1):137.

139. Ahmed S, Ahmed A, Rådegran G. Circulating biomarkers in pulmonary arterial hypertension: State-of-the-art review and future directions. JHLT Open 2024;6.

140. Wu M, Wu Y, Huang J, et al. Protein expression profile changes of lung tissue in patients with pulmonary hypertension. PeerJ 2020;8:e8153.

141. Amsallem M, Sweatt AJ, Arthur Ataam J, et al. Targeted proteomics of right heart adaptation to pulmonary arterial hypertension. Eur Respir J 2021;57(4).

142. Daly CM, Griffiths M, Simpson CE, et al. Angiostatic peptide, endostatin, predicts severity in pediatric congenital heart disease-associated pulmonary hypertension. J Am Heart Assoc 2021;10(20):e021409.

143. Simpson CE, Griffiths M, Yang J, et al. The angiostatic peptide endostatin enhances mortality risk prediction in pulmonary arterial hypertension. ERJ Open Res 2021;7(4).

144. Griffiths M, Yang J, Simpson CE, et al. ST2 is a biomarker of pediatric pulmonary arterial hypertension severity and clinical worsening. Chest 2021;160(1):297-306.

145. Simpson CE, Chen JY, Damico RL, et al. Cellular sources of interleukin-6 and associations with clinical phenotypes and outcomes in pulmonary arterial hypertension. Eur Respir J 2020;55(4).

146. Leuchte HH, El Nounou M, Tuerpe JC, et al. N-terminal pro-brain natriuretic peptide and renal insufficiency as predictors of mortality in pulmonary hypertension. Chest 2007;131(2):402-9.

147. Chakinala MM, Coyne DW, Benza RL, et al. Impact of declining renal function on outcomes in pulmonary arterial hypertension: A REVEAL registry analysis. J Heart Lung Transpl 2018;37(6):696-705.

148. Heresi GA, Tang WH, Aytekin M, Hammel J, Hazen SL, Dweik RA. Sensitive cardiac troponin I predicts poor outcomes in pulmonary arterial hypertension. Eur Respir J 2012;39(4):939-44.

149. Schuuring MJ, van Riel AC, Vis JC, et al. High-sensitivity troponin T is associated with poor outcome in adults with pulmonary arterial hypertension due to congenital heart disease. Congenit Heart Dis 2013;8(6):520-6.

150. Forfia PR, Mathai SC, Fisher MR, et al. Hyponatremia predicts right heart failure and poor survival in pulmonary arterial hypertension. Am J Respir Crit Care Med 2008;177(12):1364-9.

151. Naal T, Abuhalimeh B, Khirfan G, Dweik RA, Tang WHW, Tonelli AR. Serum chloride levels track with survival in patients with pulmonary arterial hypertension. Chest 2018;154(3):541-9.

152. Benza RL, Gomberg-Maitland M, Naeije R, Arneson CP, Lang IM. Prognostic factors associated with increased survival in patients with pulmonary arterial hypertension treated with subcutaneous treprostinil in randomized, placebo-controlled trials. J Heart Lung Transpl 2011;30(9):982-9.

153. Dhaun N, Vachiery JL, Benza RL, et al. Endothelin antagonism and uric acid levels in pulmonary arterial hypertension: clinical associations. J Heart Lung Transpl 2014;33(5):521-7.

154. Quarck R, Nawrot T, Meyns B, Delcroix M. C-reactive protein: a new predictor of adverse outcome in pulmonary arterial hypertension. J Am Coll Cardiol 2009;53(14):1211-8.

155. Lannan KL, Phipps RP, White RJ. Thrombosis, platelets, microparticles and PAH: more than a clot. Drug Discov Today 2014;19(8):1230-5.

156. Belly MJ, Tiede H, Morty RE, et al. HbA1c in pulmonary arterial hypertension: a marker of prognostic relevance? J Heart Lung Transpl 2012;31(10):1109-14.

157. Le RJ, Larsen CM, Fenstad ER, et al. Thrombocytopenia independently predicts death in idiopathic pah. Heart Lung 2019;48(1):34-8.

158. Badagliacca R, Vizza CD. Imaging risk in pulmonary arterial hypertension. Eur Respir J 2020;56(3).

159. Badagliacca R, Papa S, Valli G, et al. Echocardiography combined with cardiopulmonary exercise testing for the prediction of outcome in idiopathic pulmonary arterial hypertension. Chest 2016;150(6):1313-22.

160. Tello K, Wan J, Dalmer A, et al. Validation of the tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio for the assessment of right ventricular-arterial coupling in severe pulmonary hypertension. Circ Cardiovasc Imaging 2019;12(9):e009047.

161. Tello K, Axmann J, Ghofrani HA, et al. Relevance of the TAPSE/PASP ratio in pulmonary arterial hypertension. Int J Cardiol 2018;266:229-35.

162. Ernande L, Cottin V, Leroux PY, et al. Right isovolumic contraction velocity predicts survival in pulmonary hypertension. J Am Soc Echocardiogr 2013;26(3):297-306.

163. Badagliacca R, Reali M, Poscia R, et al. Right intraventricular dyssynchrony in idiopathic, heritable, and anorexigen-induced pulmonary arterial hypertension: clinical impact and reversibility. JACC Cardiovasc Imaging 2015;8(6):642-52.

164. Badagliacca R, Papa S, Valli G, et al. Right ventricular dyssynchrony and exercise capacity in idiopathic pulmonary arterial hypertension. Eur Respir J 2017;49(6).

165. Badagliacca R, Poscia R, Pezzuto B, et al. Prognostic relevance of right heart reverse remodeling in idiopathic pulmonary arterial hypertension. J Heart Lung Transpl 2017.

166. Badagliacca R, Papa S, Manzi G, et al. Usefulness of adding echocardiography of the right heart to risk-assessment scores in prostanoid-treated pulmonary arterial hypertension. JACC Cardiovasc Imaging 2020;13(9):2054-6.

167. Shimada YJ, Shiota M, Siegel RJ, Shiota T. Accuracy of right ventricular volumes and function determined by three-dimensional echocardiography in comparison with magnetic resonance imaging: a meta-analysis study. J Am Soc Echocardiogr 2010;23(9):943-53.

168. Hedstrom E, Bredfelt A, Radegran G, Arheden H, Ostenfeld E. Risk assessment in PAH using quantitative CMR tricuspid regurgitation: relation to heart catheterization. ESC Heart Fail 2020;7(4):1653-63.

169. Vogel-Claussen J, Skrok J, Shehata ML, et al. Right and left ventricular myocardial perfusion reserves correlate with right ventricular function and pulmonary hemodynamics in patients with pulmonary arterial hypertension. Radiology 2011;258(1):119-27.

170. Seraphim A, Knott KD, Menacho K, et al. Prognostic value of pulmonary transit time and pulmonary blood volume estimation using myocardial perfusion CMR. JACC Cardiovasc Imaging 2021;14(11):2107-19.

171. Alabed S, Saunders L, Garg P, et al. Myocardial T1-mapping and extracellular volume in pulmonary arterial hypertension: a systematic review and meta-analysis. Magn Reson Imaging 2021;79:66-75.

172. Kazimierczyk R, Malek LA, Szumowski P, et al. Prognostic value of late gadolinium enhancement mass index in patients with pulmonary arterial hypertension. Adv Med Sci 2021;66(1):28-34.

173. Swift AJ, Rajaram S, Capener D, et al. LGE patterns in pulmonary hypertension do not impact overall mortality. JACC Cardiovasc Imaging 2014;7(12):1209-17.

174. Benza R, Biederman R, Murali S, Gupta H. Role of cardiac magnetic resonance imaging in the management of patients with pulmonary arterial hypertension. J Am Coll Cardiol 2008;52(21):1683-92.

175. Gonzalez Lengua C, Agarwal C, Chokshi A, et al. Prognostic value of cardiac magnetic resonance estimates of ventriculoarterial coupling in pulmonary hypertension. JACC Cardiovasc Imaging 2020;13(10):2268-70.

176. van de Veerdonk MC, Kind T, Marcus JT, et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. J Am Coll Cardiol 2011;58(24):2511-9.

177. van der Bruggen CE, Handoko ML, Bogaard HJ, et al. The value of hemodynamic measurements or cardiac MRI in the follow-up of patients with idiopathic pulmonary arterial hypertension. Chest 2021;159(4):1575-85.

178. Baggen VJ, Leiner T, Post MC, et al. Cardiac magnetic resonance findings predicting mortality in patients with pulmonary arterial hypertension: a systematic review and meta-analysis. Eur Radiol 2016;26(11):3771-80.

179. Dong Y, Pan Z, Wang D, et al. Prognostic value of cardiac magnetic resonance-derived right ventricular remodeling parameters in pulmonary hypertension: a systematic review and meta-analysis. Circ Cardiovasc Imaging 2020;13(7):e010568.

180. Alabed S, Shahin Y, Garg P, et al. Cardiac-MRI predicts clinical worsening and mortality in pulmonary arterial hypertension: a systematic review and meta-analysis. JACC Cardiovasc Imaging 2021;14(5):931-42.

181. Swift AJ, Capener D, Johns C, et al. Magnetic resonance imaging in the prognostic evaluation of patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 2017;196(2):228-39.

182. Bredfelt A, Radegran G, Hesselstrand R, Arheden H, Ostenfeld E. Increased right atrial volume measured with cardiac magnetic resonance is associated with worse clinical outcome in patients with pre-capillary pulmonary hypertension. ESC Heart Fail 2018;5(5):864-75.

183. van Wolferen SA, Marcus JT, Boonstra A, et al. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. Eur Heart J 2007;28(10):1250-7.

184. van Wolferen SA, van de Veerdonk MC, Mauritz GJ, et al. Clinically significant change in stroke volume in pulmonary hypertension. Chest 2011;139(5):1003-9.

185. Lewis RA, Johns CS, Cogliano M, et al. Identification of cardiac magnetic resonance imaging thresholds for risk stratification in pulmonary arterial hypertension. Am J Respir Crit Care Med 2020;201(4):458-68.

186. Wang L, Chen X, Wan K, et al. Diagnostic and prognostic value of right ventricular eccentricity index in pulmonary artery hypertension. Pulm Circ 2020;10(2). 2045894019899778.

187. Freed BH, Gomberg-Maitland M, Chandra S, et al. Late gadolinium enhancement cardiovascular magnetic resonance predicts clinical worsening in patients with pulmonary hypertension. J Cardiovasc Magn Reson 2012;14(1):11.

188. Asano R, Ogo T, Morita Y, et al. Prognostic value of right ventricular native T1 mapping in pulmonary arterial hypertension. PLoS One 2021;16(11):e0260456.

189. Dawes TJW, de Marvao A, Shi W, et al. Machine learning of three-dimensional right ventricular motion enables outcome prediction in pulmonary hypertension: a cardiac MR imaging study. Radiology 2017;283(2):381-90.

190. Zhao X, Leng S, Tan RS, et al. Right ventricular energetic biomarkers from 4D Flow CMR are associated with exertional capacity in pulmonary arterial hypertension. J Cardiovasc Magn Reson 2022;24(1):61.

191. Leng S, Dong Y, Wu Y, et al. Impaired cardiovascular magnetic resonance-derived rapid semiautomated right atrial longitudinal strain is associated with decompensated hemodynamics in pulmonary arterial hypertension. Circ Cardiovasc Imaging 2019;12(5):e008582.

192. Peacock AJ, Crawley S, McLure L, et al. Changes in right ventricular function measured by cardiac magnetic resonance imaging in patients receiving pulmonary arterial hypertension-targeted therapy: the EURO-MR study. Circ Cardiovasc Imaging 2014;7(1):107-14.

193. Swift AJ, Capener D, Hammerton C, et al. Right ventricular sex differences in patients with idiopathic pulmonary arterial hypertension characterised by magnetic resonance imaging: pair-matched case controlled study. PLoS One 2015;10(5):e0127415.

194. Ventetuolo CE, Ouyang P, Bluemke DA, et al. Sex hormones are associated with right ventricular structure and function: the MESA-right ventricle study. Am J Respir Crit Care Med 2011;183(5):659-67.

195. Badagliacca R, Poscia R, Pezzuto B, et al. Right ventricular remodeling in idiopathic pulmonary arterial hypertension: adaptive versus maladaptive morphology. J Heart Lung Transpl 2015;34(3):395-403.

196. Badagliacca R, Poscia R, Pezzuto B, et al. Right ventricular concentric hypertrophy and clinical worsening in idiopathic pulmonary arterial hypertension. J Heart Lung Transpl 2016;35(11):1321-9.

197. Grapsa J, Tan TC, Nunes MCP, et al. Prognostic impact of right ventricular mass change in patients with idiopathic pulmonary arterial hypertension. Int J Cardiol 2020;304:172-4.

198. Goh ZM, Alabed S, Shahin Y, et al. Right ventricular adaptation assessed using cardiac magnetic resonance predicts survival in pulmonary arterial hypertension. JACC Cardiovasc Imaging 2021;14(6):1271-2.

199. Goh ZM, Balasubramanian N, Alabed S, et al. Right ventricular remodelling in pulmonary arterial hypertension predicts treatment response. Heart 2022;108(17):1392-400.

200. Sanz J, Garcia-Alvarez A, Fernandez-Friera L, et al. Right ventriculo-arterial coupling in pulmonary hypertension: a magnetic resonance study. Heart 2012;98(3):238-43.

201. Kazimierczyk R, Szumowski P, Nekolla SG, et al. The impact of specific pulmonary arterial hypertension therapy on cardiac fluorodeoxyglucose distribution in PET/MRI hybrid imaging-follow-up study. EJNMMI Res 2023;13(1):20.

202. Colalillo A, Hoffmann-Vold AM, Pellicano C, et al. The role of TAPSE/sPAP ratio in predicting pulmonary hypertension and mortality in the systemic sclerosis EUSTAR cohort. Autoimmun Rev 2023;22(4):103290.

203. Colak A, Kumral Z, Kis M, et al. The usefulness of the TAPSE/sPAP ratio for predicting survival in medically treated chronic thromboembolic pulmonary hypertension. Turk Kardiyol Dern Ars 2023;51(7):470-7.

204. Tello K, Dalmer A, Axmann J, et al. Reserve of right ventricular-arterial coupling in the setting of chronic overload. Circ Heart Fail 2019;12(1):e005512.

205. Vanderpool RR, Pinsky MR, Naeije R, et al. RV-pulmonary arterial coupling predicts outcome in patients referred for pulmonary hypertension. Heart 2015;101(1):37-43.

206. Brewis MJ, Bellofiore A, Vanderpool RR, et al. Imaging right ventricular function to predict outcome in pulmonary arterial hypertension. Int J Cardiol 2016;218:206-11.

207. Jone PN, Schafer M, Pan Z, Ivy DD. Right ventricular-arterial coupling ratio derived from 3-dimensional echocardiography predicts outcomes in pediatric pulmonary hypertension. Circ Cardiovasc Imaging 2019;12(1):e008176.

208. Kazimierczyk R, Malek LA, Szumowski P, et al. Multimodal assessment of right ventricle overload-metabolic and clinical consequences in pulmonary arterial hypertension. J Cardiovasc Magn Reson 2021;23(1):49.

209. Guignabert C, Dorfmuller P. Pathology and pathobiology of pulmonary hypertension. Semin Respir Crit Care Med 2017;38(5):571-84.

210. Nahrendorf M, Frantz S, Swirski FK, et al. Imaging systemic inflammatory networks in ischemic heart disease. J Am Coll Cardiol 2015;65(15):1583-91.

211. Trujillo JO, Tura-Ceide O, Pavia J, et al. 18-FDG uptake on PET-CT and metabolism in pulmonary arterial hypertension. European Respiratory Journal 2021. p. PA588.

212. Maier A, Liao SL, Lescure T, et al. Pulmonary artery (18)F-fluorodeoxyglucose uptake by PET/CMR as a marker of pulmonary hypertension in sarcoidosis. JACC Cardiovasc Imaging 2022;15(1):108-20.

213. Park JB, Suh M, Park JY, et al. Assessment of inflammation in pulmonary artery hypertension by (68)Ga-mannosylated human serum albumin. Am J Respir Crit Care Med 2020;201(1):95-106.

214. Botros L, Jansen SMA, Ashek A, et al. Application of [18F]FLT-PET in pulmonary arterial hypertension: a clinical study in pulmonary arterial hypertension patients and unaffected bone morphogenetic protein receptor type 2 mutation carriers. Pulm Circ 2021;11(3). 20458940211028017.

215. Weatherald J, Boucly A, Chemla D, et al. Prognostic value of follow-up hemodynamic variables after initial management in pulmonary arterial hypertension. Circulation 2018;137(7):693-704.

216. Weatherald J, Boucly A, Launay D, et al. Haemodynamics and serial risk assessment in systemic sclerosis associated pulmonary arterial hypertension. Eur Respir J 2018;52(4).

217. Galie N, Jansa P, Pulido T, et al. SERAPHIN haemodynamic substudy: the effect of the dual endothelin receptor antagonist macitentan on haemodynamic parameters and NT-proBNP levels and their association with disease progression in patients with pulmonary arterial hypertension. Eur Heart J 2017;38(15):1147-55.

218. Weatherald J, Boucly A, Peters A, et al. The evolving landscape of pulmonary arterial hypertension clinical trials. Lancet 2022;400(10366):1884-98.

219. Badagliacca R, Vizza CD, Lang I, et al. Pulmonary pressure recovery in idiopathic, hereditary and drug and toxin-induced pulmonary arterial hypertension: determinants and clinical impact. Vasc Pharm 2022;146:107099.

220. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991;115(5):343-9.

221. Kozu K, Sugimura K, Aoki T, et al. Sex differences in hemodynamic responses and long-term survival to optimal medical therapy in patients with pulmonary arterial hypertension. Heart Vessels 2018;33(8):939-47.

222. Bartolome SD, Sood N, Shah TG, Styrvoky K, Torres F, Chin KM. Mortality in patients with pulmonary arterial hypertension treated with continuous prostanoids. Chest 2018;154(3):532-40.

223. Khirfan G, Almoushref A, Naal T, et al. Mixed venous oxygen saturation is a better prognosticator than cardiac index in pulmonary arterial hypertension. Chest 2020;158(6):2546-55.

224. Hassan HJ, Naranjo M, Kazzi B, et al. Risk assessment of systemic sclerosis-associated pulmonary arterial hypertension: cardiac index versus stroke volume index. Eur Respir J 2022;60(3).

225. Vonk Noordegraaf A, Chin KM, Haddad F, et al. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. Eur Respir J 2019;53(1).

226. Vonk Noordegraaf A, Westerhof BE, Westerhof N. The relationship between the right ventricle and its load in pulmonary hypertension. J Am Coll Cardiol 2017;69(2):236-43.

227. Mahapatra S, Nishimura RA, Sorajja P, Cha S, McGoon MD. Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. J Am Coll Cardiol 2006;47(4):799-803.

228. Campo A, Mathai SC, Le Pavec J, et al. Hemodynamic predictors of survival in scleroderma-related pulmonary arterial hypertension. Am J Respir Crit Care Med 2010;182(2):252-60.

229. Brittain EL, Pugh ME, Wheeler LA, et al. Shorter survival in familial versus idiopathic pulmonary arterial hypertension is associated with hemodynamic markers of impaired right ventricular function. Pulm Circ 2013;3(3):589-98.

230. Al-Naamani N, Preston IR, Hill NS, Roberts KE. The prognostic significance of pulmonary arterial capacitance in pulmonary arterial hypertension: single-center experience. Pulm Circ 2016;6(4):608-10.

231. Ghio S, D'Alto M, Badagliacca R, et al. Prognostic relevance of pulmonary arterial compliance after therapy initiation or escalation in patients with pulmonary arterial hypertension. Int J Cardiol 2017;230:53-8.

232. Medrek SK, Kloefkorn C, Nguyen DTM, Graviss EA, Frost AE, Safdar Z. Longitudinal change in pulmonary arterial capacitance as an indicator of prognosis and response to therapy and in pulmonary arterial hypertension. Pulm Circ 2017;7(2):399-408.

233. Thenappan T, Al-Naamani N, Ghio S, et al. Effect of riociguat on pulmonary arterial compliance in the PATENT and CHEST studies. Pulm Circ 2020;10(4). 2045894020963836.

234. Guo X, Lai J, Wang H, et al. Predictive value of pulmonary arterial compliance in systemic lupus erythematosus patients with pulmonary arterial hypertension. Hypertension 2020;76(4):1161-8.

235. Cheng XL, Liu ZH, Gu Q, et al. Prognostic value of pulmonary artery compliance in patients with pulmonary arterial hypertension associated with adult congenital heart disease. Int Heart J 2017;58(5):731-8.

236. Suzuki S, Asano R, Aoki T, et al. Prognostic impact of follow-up pulmonary vascular resistance in pulmonary arterial hypertension. Open Heart 2022;9(1).

237. Sung SH, Yeh WY, Chiang CE, et al. The prognostic significance of the alterations of pulmonary hemodynamics in patients with pulmonary arterial hypertension: a meta-regression analysis of randomized controlled trials. Syst Rev 2021;10(1):284.

238. Bayram Z, Dogan C, Efe SC, et al. Prognostic importance of pulmonary artery pulsatility index and right ventricular stroke work index in end-stage heart failure patients. Cardiology 2022;147(2):143-53.

239. Lim Y, Low TT, Chan SP, et al. Does pulmonary artery pulsatility index predict mortality in pulmonary arterial hypertension? ESC Heart Fail 2021;8(5):3835-44.

240. Mazimba S, Welch TS, Mwansa H, et al. Haemodynamically derived pulmonary artery pulsatility index predicts mortality in pulmonary arterial hypertension. Heart Lung Circ 2019;28(5):752-60.

241. Clapham KR, Highland KB, Rao Y, Fares WH. Reduced RVSWI is associated with increased mortality in connective tissue disease associated pulmonary arterial hypertension. Front Cardiovasc Med 2020;7:77.

242. Sinning C, Harbaum L, Schrage B, et al. Right ventricular index for risk stratification of patients with pulmonary arterial hypertension. Respiration 2018;96(3):249-58.

243. Trip P, Rain S, Handoko ML, et al. Clinical relevance of right ventricular diastolic stiffness in pulmonary hypertension. Eur Respir J 2015;45(6):1603-12.

244. Hsu S, Simpson CE, Houston BA, et al. Multi-beat right ventricular-arterial coupling predicts clinical worsening in pulmonary arterial hypertension. J Am Heart Assoc 2020;9(10):e016031.

245. Brewis MJ, Bellofiore A, Vanderpool RR, et al. Imaging right ventricular function to predict outcome in pulmonary arterial hypertension. Int J Cardiol 2016;218:206-11.

246. Chaouat A, Sitbon O, Mercy M, et al. Prognostic value of exercise pulmonary haemodynamics in pulmonary arterial hypertension. Eur Respir J 2014;44(3):704-13.

247. Hasler ED, Muller-Mottet S, Furian M, et al. Pressure-flow during exercise catheterization predicts survival in pulmonary hypertension. Chest 2016;150(1):57-67.

248. D'Alto M, Motoji Y, Romeo E, et al. Fluid challenge predicts clinical worsening in pulmonary arterial hypertension. Int J Cardiol 2018;261:167-71.

249. Chew JD, Loyd JE, Austin ED. Genetics of pulmonary arterial hypertension. Semin Respir Crit Care Med 2017;38(5):585-95.

250. Ma L, Chung WK. The role of genetics in pulmonary arterial hypertension. J Pathol 2017;241(2):273-80.

251. Austin ED, Aldred MA, Alotaibi M, et al. Genetics and precision genomics approaches to pulmonary hypertension. Eur Respir J 2024;64(4).

252. Varghese NP, Padhye AA, Magoulas PL, Mallory GB, Ruiz FE, Sahay S. The cascade screening in heritable forms of pulmonary arterial hypertension. Pulm Circ 2023;13(3):e12259.

253. Herman JG, Baylin SB. Gene silencing in cancer in association with promoter hypermethylation. N Engl J Med 2003;349(21):2042-54.

254. Benincasa G, Maron BA, Affinito O, et al. Association between circulating CD4(+) T cell methylation signatures of network-oriented SOCS3 gene and hemodynamics in patients suffering pulmonary arterial hypertension. J Cardiovasc Transl Res 2022.

255. Southgate L, Machado RD, Graf S, Morrell NW. Molecular genetic framework underlying pulmonary arterial hypertension. Nat Rev Cardiol 2020;17(2):85-95.

256. Welch CL, Chung WK. Genetics and other omics in pediatric pulmonary arterial hypertension. Chest 2020;157(5):1287-95.

257. Morrell NW, Aldred MA, Chung WK, et al. Genetics and genomics of pulmonary arterial hypertension. Eur Respir J 2019;53(1).

258. International PPHC, Lane KB, Machado RD, et al. Heterozygous germline mutations in BMPR2, encoding a TGF-beta receptor, cause familial primary pulmonary hypertension. Nat Genet 2000;26(1):81-4.

259. Lane KB, Pauciulo MW, Thomson JR, et al. Heterozygous germline mutations in BMPR2, encoding a TGF-beta receptor, cause familial primary pulmonary hypertension. Nat Genet 2000;26(1):81-4.

260. Nichols WC, Koller DL, Slovis B, et al. Localization of the gene for familial primary pulmonary hypertension to chromosome 2q31-32. Nat Genet 1997;15(3):277-80.

261 Zhu N., Pauciulo M.W., Welch C.L., et al. Novel risk genes and mechanisms implicated by exome sequencing of 2,572 individuals with pulmonary arterial hypertension. Submitted to biorxivorg. 2019.

262. Evans JD, Girerd B, Montani D, et al. BMPR2 mutations and survival in pulmonary arterial hypertension: an individual participant data meta-analysis. Lancet Respir Med 2016;4(2):129-37.

263. Benza RL, Gomberg-Maitland M, Demarco T, et al. Endothelin-1 pathway polymorphisms and outcomes in pulmonary arterial hypertension. Am J Respir Crit Care Med 2015;192(11):1345-54.

264. Rhodes CJ, Batai K, Bleda M, et al. Genetic determinants of risk in pulmonary arterial hypertension: international genome-wide association studies and meta-analysis. Lancet Respir Med 2018.

265. Karolak JA, Welch CL, Mosimann C, et al. Molecular function and contribution of TBX4 in development and disease. Am J Respir Crit Care Med 2022.

266. Damico R, Kolb TM, Valera L, et al. Serum endostatin is a genetically determined predictor of survival in pulmonary arterial hypertension. Am J Respir Crit Care Med 2015;191(2):208-18.

267. Simpson CE, Griffiths M, Yang J, et al. COL18A1 genotypic associations with endostatin levels and clinical features in pulmonary arterial hypertension: a quantitative trait association study. ERJ Open Res 2022;8(2).

268. Ventetuolo CE, Mitra N, Wan F, et al. Oestradiol metabolism and androgen receptor genotypes are associated with right ventricular function. Eur Respir J 2016;47(2):553-63.

269. Willers ED, Newman JH, Loyd JE, et al. Serotonin transporter polymorphisms in familial and idiopathic pulmonary arterial hypertension. Am J Respir Crit Care Med 2006;173(7):798-802.

270. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Pulmonary function in primary pulmonary hypertension. J Am Coll Cardiol 2003;41(6):1028-35.

271. Meyer FJ, Ewert R, Hoeper MM, et al. Peripheral airway obstruction in primary pulmonary hypertension. Thorax 2002;57(6):473-6.

272. Lewis RA, Thompson AAR, Billings CG, et al. Mild parenchymal lung disease and/or low diffusion capacity impacts survival and treatment response in patients diagnosed with idiopathic pulmonary arterial hypertension. Eur Respir J 2020;55(6).

273. Frantz RP, Benza RL, Channick RN, et al. TORREY, a Phase 2 study to evaluate the efficacy and safety of inhaled seralutinib for the treatment of pulmonary arterial hypertension. Pulm Circ 2021;11(4). 20458940211057071.

274. Chung L, Liu J, Parsons L, et al. Characterization of connective tissue disease associated pulmonary arterial hypertension from the reveal registry: identifying systemic sclerosis as a unique phenotype. Chest 2010.

275. Chandra S, Shah SJ, Thenappan T, Archer SL, Rich S, Gomberg-Maitland M. Carbon monoxide diffusing capacity and mortality in pulmonary arterial hypertension. J Heart Lung Transpl 2010;29(2):181-7.

276. Trip P, Nossent EJ, de Man FS, et al. Severely reduced diffusion capacity in idiopathic pulmonary arterial hypertension: patient characteristics and treatment responses. Eur Respir J 2013;42(6):1575-85.

277. Hoeper MM, Pausch C, Grunig E, et al. Idiopathic pulmonary arterial hypertension phenotypes determined by cluster analysis from the COMPERA registry. J Heart Lung Transpl 2020;39(12):1435-44.

278. Hoeper MM, Dwivedi K, Pausch C, et al. Phenotyping of idiopathic pulmonary arterial hypertension: a registry analysis. Lancet Respir Med 2022;10(10):937-48.

279. Olsson KM, Fuge J, Park DH, et al. Effects of sotatercept on lung diffusion capacity and blood gases in patients with pulmonary arterial hypertension. Eur Respir J 2023;62(2).

280. McGoon MD, Miller DP. REVEAL: a contemporary US pulmonary arterial hypertension registry. Eur Respir Rev 2012;21(123):8-18.

281. Thenappan T, Glassner C, Gomberg-Maitland M. Validation of the pulmonary hypertension connection equation for survival prediction in pulmonary arterial hypertension. Chest 2012;141(3):642-50.

282. Hoeper MM, Markevych I, Spiekerkoetter E, Welte T, Niedermeyer J. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. Eur Respir J 2005;26(5):858-63.

283. McLaughlin VV, McGoon MD. Pulmonary arterial hypertension. Circulation 2006;114(13):1417-31.

284. Benza Raymond L, Miller Dave P, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension. Circulation 2010;122(2):164-72.

285. Kylhammar D, Hjalmarsson C, Hesselstrand R, et al. Predicting mortality during long-term follow-up in pulmonary arterial hypertension. ERJ Open Res 2021;7(2).

286. Kanwar MK, Gomberg-Maitland M, Hoeper M, et al. Risk stratification in pulmonary arterial hypertension using Bayesian analysis. Eur Respir J 2020;56(2).

287. Boucly A, Beurnier A, Turquier S, et al. Risk stratification refinements with inclusion of haemodynamic variables at follow-up in patients with pulmonary arterial hypertension. Eur Respir J 2024.

288 Kraisangka J., Druzdzel M.J., Lohmueller L.C., Kanwar M.K., Antaki J.F., Benza R.L., editors. Bayesian Network vs. Cox's Proportional Hazard Model of PAH Risk: A Comparison. Artificial Intelligence in Medicine: 17th Conference on Artificial Intelligence in Medicine, AIME 2019, Poznan, Poland, June 26–29, 2019, Proceedings 17; 2019: Springer.

289. Hoeper MM, Pittrow D, Opitz C, et al. Risk assessment in pulmonary arterial hypertension. Eur Respir J 2018;51(3).

290. Bartenstein P, Saxer S, Appenzeller P, Lichtblau M, Schwarz EI, Ulrich S. Risk factor profiles achieved with medical therapy in prevalent patients with pulmonary arterial and distal chronic thromboembolic pulmonary hypertension. Respiration 2018;96(2):127-37.

291. Mercurio V, Diab N, Peloquin G, et al. Risk assessment in scleroderma patients with newly diagnosed pulmonary arterial hypertension: application of the ESC/ERS risk prediction model. Eur Respir J 2018;52(4).

292. Boucly A, Weatherald J, Savale L, et al. External validation of a refined four-stratum risk assessment score from the French pulmonary hypertension registry. Eur Respir J 2022;59(6):2102419.

293. Pausch C, Pittrow D, Hoeper MM, Huscher D. Performance of the ESC/ERS 4-strata risk stratification model for pulmonary arterial hypertension with missing variables. Eur Respir J 2023;62(5).

294. Hoeper MM, Pittrow D, Opitz C, et al. Risk assessment in pulmonary arterial hypertension. Eur Respir J 2018;51(3):1702606.

295. Ahmed A, Ahmed S, Radegran G. Risk assessment in pulmonary arterial hypertension: a step towards clinical implementation based on the 2022 ESC/ERS pulmonary hypertension guidelines. Pulm Circ 2023;13(2):e12253.

296. Farber HW, Miller DP, Poms AD, et al. Five-year outcomes of patients enrolled in the REVEAL registry. Chest 2015;148(4):1043-54.

297. Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. Chest 2012;141(2):354-62.

298. Benza RL, Farber HW, Frost A, et al. REVEAL risk scores applied to riociguat-treated patients in PATENT-2: Impact of changes in risk score on survival. J Heart Lung Transpl 2018;37(4):513-9.

299. Benza RL, Farber HW, Frost A, et al. REVEAL risk score in patients with chronic thromboembolic pulmonary hypertension receiving riociguat. J Heart Lung Transpl 2018;37(7):836-43.

300. Yogeswaran A, Gall H, Funderich M, et al. Comparison of contemporary risk scores in all groups of pulmonary hypertension: a pulmonary vascular research institute GoDeep meta-registry analysis. Chest 2024.

301. Anderson JJ, Lau EM, Lavender M, et al. Retrospective validation of the REVEAL 2.0 risk score with the Australian and New Zealand pulmonary hypertension registry cohort. Chest 2020;157(1):162-72.

302. Benza RL, Farber HW, Frost AE, et al. Application of the REVEAL risk score calculator 2.0 in the PATENT study. Int J Cardiol 2021;332:189-92.

303. Benza RL, Boucly A, Farber HW, et al. Change in REVEAL Lite 2 risk score predicts outcomes in patients with pulmonary arterial hypertension in the PATENT study. J Heart Lung Transpl 2022;41(3):411-20.

304. Tonelli AR, Sahay S, Gordon KW, et al. Impact of inhaled treprostinil on risk stratification with noninvasive parameters: a post hoc analysis of the TRIUMPH and BEAT studies. Pulm Circ 2020;10(4). 2045894020977025.

305. McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. J Am Coll Cardiol 2010;55(18):1915-22.

306. Spilimbergo FB, Pirath Rodrigues R, Credidio Dias-Pinto M, et al. Risk assessment validation in patients with pulmonary arterial hypertension: Data from a Southern Brazil registry (RESPHIRAR study). Pulm Circ 2023;13(1):e12193.

307. Benza M, a Raymond L, Chin, MD,b Kelly M, Gaine, MD,c Sean, et al. REVEAL Lite 2 risk status is associated with long-term outcomes in patients with pulmonary arterial hypertension from the GRIPHON study: a post-hoc analysis. J Heart Lung Transpl 2024.

308. Sahay S, Villasmil Hernandez N, Wang F, et al. Comparison between REVEAL Lite 2 and COMPERA 2.0 for risk stratification in pulmonary arterial hypertension. Chest 2024.

309. Wilson M, Keeley J, Kingman M, Wang J, Rogers F. Current clinical utilization of risk assessment tools in pulmonary arterial hypertension: a descriptive survey of facilitation strategies, patterns, and barriers to use in the United States. Pulm Circ 2020;10(3). 2045894020950186.

310. Ahmed A, Ahmed S, Radegran G. Risk assessment in pulmonary arterial hypertension patients with multiple comorbidities and/or advanced age-Where do we stand and what's next? Pulm Circ 2023;13(4):e12314.

311. Hjalmarsson C, Radegran G, Kylhammar D, et al. Impact of age and comorbidity on risk stratification in idiopathic pulmonary arterial hypertension. Eur Respir J 2018;51(5).

312. Cascino TM, Sahay S, Moles VM, McLaughlin VV. A new day has come: sotatercept for the treatment of pulmonary arterial hypertension. J Heart Lung Transpl 2024.

313. Ghio S, Mercurio V, Fortuni F, et al. A comprehensive echocardiographic method for risk stratification in pulmonary arterial hypertension. Eur Respir J 2020;56(3).

314. El-Kersh K, Zhao C, Elliott G, et al. Derivation of a risk score (REVEAL-ECHO) based on echocardiographic parameters of patients with pulmonary arterial hypertension. Chest 2023;163(5):1232-44.

315. Sahay S, Bhatt J, Beshay S, et al. E-REVEAL Lite 2.0 scoring for early prediction of disease progression in pulmonary arterial hypertension. Pulm Circ 2022;12(1):e12026.

316. Vicenzi M, Caravita S, Rota I, et al. The added value of right ventricular function normalized for afterload to improve risk stratification of patients with pulmonary arterial hypertension. PLoS One 2022;17(5):e0265059.

317. Ostermann J, Pott J, Hennigs JK, et al. Residual risk identified in routine noninvasive follow-up assessments in pulmonary arterial hypertension. ERJ Open Res 2023;9(3).

318. Fauvel C, Raitiere O, Boucly A, et al. Interest of TAPSE/sPAP ratio for noninvasive pulmonary arterial hypertension risk assessment. J Heart Lung Transpl 2022;41(12):1761-72.

319. Forfia P, Benza R, D'Alto M, et al. The heart of the matter: right heart imaging indicators for treatment escalation in pulmonary arterial hypertension. Pulm Circ 2023;13(2):e12240.

320. Badagliacca R, Ghio S, D'Alto M, et al. Relevance of echocardiography-derived phenotyping in pulmonary arterial hypertension patients treated with initial oral combination therapy. Am J Respir Crit Care Med 2024.

321. Chin KM, Gaine SP, Gerges C, et al. Treatment algorithm for pulmonary arterial hypertension. Eur Respir J 2024.

322. Sahay S, Chakinala MM, Kim NH, Preston IR, Thenappan T, McLaughlin VV. Contemporary treatment of pulmonary arterial hypertension: a US perspective. Am J Respir Crit Care Med 2024.

323. Rubin LJ, Mendoza J, Hood M, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. Ann Intern Med 1990;112(7):485-91.

324. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996;334(5):296-301.

325. Fritz JS, Blair C, Oudiz RJ, et al. Baseline and follow-up 6-min walk distance and brain natriuretic peptide predict 2-year mortality in pulmonary arterial hypertension. Chest 2013;143(2):315-23.

326. Hoeper MM, Ewert R, Jansa P, et al. Randomized, multicenter study to assess the effects of different doses of sildenafil on mortality in adults with pulmonary arterial hypertension. Circulation 2024.

327. Weatherald J, Fleming TR, Wilkins MR, et al. Clinical trial design, end-points, and emerging therapies in pulmonary arterial hypertension. Eur Respir J 2024.

328. White RJ, Jerjes-Sanchez C, Bohns Meyer GM, et al. Combination therapy with oral treprostinil for pulmonary arterial hypertension. a double-blind placebo-controlled clinical trial. Am J Respir Crit Care Med 2020;201(6):707-17.

329. Hoeper MM, Al-Hiti H, Benza RL, et al. Switching to riociguat versus maintenance therapy with phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension (REPLACE): a multicentre, open-label, randomised controlled trial. Lancet Respir Med 2021;9(6):573-84.

330. Ghofrani HA, Galie N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 2013;369(4):330-40.

331. Rubin LJ, Galie N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension: a long-term extension study (PATENT-2). Eur Respir J 2015;45(5):1303-13.

332. Humbert M, Farber HW, Ghofrani HA, et al. Risk assessment in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Eur Respir J 2019;53(6).

333. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med 2015;373(26):2522-33.

334. Sitbon O, Chin KM, Channick RN, et al. Risk assessment in pulmonary arterial hypertension: Insights from the GRIPHON study. J Heart Lung Transpl 2020;39(4):300-9.

335. Sitbon O, Cottin V, Canuet M, et al. Initial combination therapy of macitentan and tadalafil in pulmonary arterial hypertension. Eur Respir J 2020;56(3).

336. Weatherald J, Boucly A, Sahay S, Humbert M, Sitbon O. 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 2018;197(7):860-8.

337. Vansteelandt S, Linder M, Vandenberghe S, Steen J, Madsen J. Mediation analysis of time-to-event endpoints accounting for repeatedly measured mediators subject to time-varying confounding. Stat Med 2019;38(24):4828-40.

338. Sitbon O, Nikkho S, Benza R, et al. Novel composite clinical endpoints and risk scores used in clinical trials in pulmonary arterial hypertension. Pulm Circ 2020;10(4). 2045894020962960.

339. Fauvel C, White RJ, Vanderpool RR, et al. Risk stratification in pulmonary arterial hypertension: perhaps simple is not best? Chest 2023.

340. Ploegstra M-J, Zijlstra WMH, Douwes JM, Hillege HL, Berger RMF. Prognostic factors in pediatric pulmonary arterial hypertension: a systematic review and meta-analysis. Int J Cardiol 2015;184:198-207.

341. Ploegstra MJ, Douwes JM, Roofthooft MT, Zijlstra WM, Hillege HL, Berger RM. Identification of treatment goals in paediatric pulmonary arterial hypertension. Eur Respir J 2014;44(6):1616-26.

342. Rosenzweig EB, Abman SH, Adatia I, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J 2019;53(1):1801916.

343. Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: guidelines From the American Heart Association and American Thoracic Society. Circulation 2015;132(21):2037-99.

344. Hansmann G, Koestenberger M, Alastalo T-P, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Heart Lung Transplant 2019;38(9):879-901.

345. Haarman MG, Douwes JM, Ploegstra M-J, et al. The clinical value of proposed risk stratification tools in pediatric pulmonary arterial hypertension. Am J Respir Crit Care Med 2019;200(10):1312-5.

346. Lokhorst C, van der Werf S, Berger RMF, Douwes JM. Risk stratification in adult and pediatric pulmonary arterial hypertension: a systematic review. Front Cardiovasc Med 2022;9.

347. Lokhorst C, van der Werf S, Berger RMF, Douwes JM. Prognostic value of serial risk stratification in adult and pediatric pulmonary arterial hypertension: a systematic review. J Am Heart Assoc 2024;13(13):e034151.

348. Lammers AE, Hislop AA, Flynn Y, Haworth SG. The 6-minute walk test: normal values for children of 4-11 years of age. Arch Dis Child 2008;93(6):464-8.

349. Mylius CF, Paap D, Takken T. Reference value for the 6-minute walk test in children and adolescents: a systematic review. Expert Rev Respir Med 2016;10(12):1335-52.

350. Gavotto A, Mura T, Rhodes J, et al. Reference values of aerobic fitness in the contemporary paediatric population. Eur J Prev Cardiol 2023;30(9):820-9.

351. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: a national cohort study. Heart 2010;96(17):1401-6.

352. Berger RM, Beghetti M, Humpl T, et al. Clinical features of paediatric pulmonary hypertension: a registry study. Lancet 2012;379(9815):537-46.

353. Jone PN, Hinzman J, Wagner BD, Ivy DD, Younoszai A. Right ventricular to left ventricular diameter ratio at end-systole in evaluating outcomes in children with pulmonary hypertension. J Am Soc Echocardiogr 2014;27(2):172-8.

354. Kassem E, Humpl T, Friedberg MK. Prognostic significance of 2-dimensional, M-mode, and Doppler echo indices of right ventricular function in children with pulmonary arterial hypertension. Am Heart J 2013;165(6):1024-31.

355. Koestenberger M, Ravekes W, Everett AD, et al. Right ventricular function in infants, children and adolescents: reference values of the tricuspid annular plane systolic excursion (TAPSE) in 640 healthy patients and calculation of z score values. J Am Soc Echocardiogr 2009;22(6):715-9.

356. Said F, Haarman MG, Roofthooft MTR, Hillege HL, Ploegstra MJ, Berger RMF. Serial measurements of N-terminal Pro-B-type natriuretic peptide serum level for monitoring pulmonary arterial hypertension in children. J Pedia 2020;220:139-45.

357. Ten Kate CA, Tibboel D, Kraemer US. B-type natriuretic peptide as a parameter for pulmonary hypertension in children. A systematic review. Eur J Pediatr 2015;174(10):1267-75.

358. Griffiths M, Yang J, Simpson CE, et al. ST2 is a biomarker of pediatric pulmonary arterial hypertension severity and clinical worsening. Chest 2021.

359. Li G, Li Y, Tan X-Q, et al. Plasma growth differentiation factor-15 is a potential biomarker for pediatric pulmonary arterial hypertension associated with congenital heart disease. Pediatr Cardiol 2017;38(8):1620-6.

360. Chen JY, Griffiths M, Yang J, et al. Elevated interleukin-6 levels predict clinical worsening in pediatric pulmonary arterial hypertension. J Pediatr 2020;223:164-9. .e1.

361. Leberkühne LJ, Ploegstra MJ, Douwes JM, et al. Serially measured uric acid levels predict disease severity and outcome in pediatric pulmonary arterial hypertension. Am J Respir Crit Care Med 2017;195(3):401-4.

362. Griffiths M, Yang J, Vaidya D, et al. Biomarkers of pulmonary hypertension are altered in children with down syndrome and pulmonary hypertension. J Pediatr 2021.

363. Welch CL, Chung WK. Genetics and genomics of pediatric pulmonary arterial hypertension. Genes 2020;11(10):1213.

364. Zhu N, Gonzaga-Jauregui C, Welch CL, et al. Exome sequencing in children with pulmonary arterial hypertension demonstrates differences compared with adults. Circ: Genom Precis Med 2018;11(4).

365. Zhu N, Welch CL, Wang J, et al. Rare variants in SOX17 are associated with pulmonary arterial hypertension with congenital heart disease. Genome Med 2018;10(1).

366. Haarman MG, Kerstjens-Frederikse WS, Berger RMF. TBX4 variants and pulmonary diseases: getting out of the 'Box'. Curr Opin Pulm Med 2020;26(3):277-84.

367. Thoré P, Girerd B, Jaïs X, et al. Phenotype and outcome of pulmonary arterial hypertension patients carrying a TBX4 mutation. Eur Respir J 2020;55(5):1902340.

368. Bush D, Galambos C, Ivy DD, Abman SH, Wolter-Warmerdam K, Hickey F. Clinical characteristics and risk factors for developing pulmonary hypertension in children with down syndrome. J Pedia 2018;202:212-9. e2.

369. Rosenzweig EB, Bates A, Mullen MP, et al. Cardiac catheterization and hemodynamics in a multicenter cohort of children with pulmonary hypertension. Ann Am Thorac Soc 2022.

370. Ollivier C, Sun H, Amchin W, et al. New strategies for the conduct of clinical trials in pediatric pulmonary arterial hypertension: outcome of a multistakeholder meeting with patients, academia, industry, and regulators, held at the European Medicines Agency on Monday, June 12, 2017. J Am Heart Assoc 2019;8(10):e011306.

371. Thenappan T, Shah SJ, Rich S, Gomberg-Maitland M. A USA-based registry for pulmonary arterial hypertension: 1982-2006. Eur Respir J 2007;30(6):1103-10.

372. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest 2012;142(2):448-56.

373. Galie N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J 2019;53(1).

374. Cogswell R, Kobashigawa E, McGlothlin D, Shaw R, De Marco T. Validation of the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL) pulmonary hypertension prediction model in a unique population and utility in the prediction of long-term survival. J Heart Lung Transpl 2012;31(11):1165-70.

375. Ling Y, Johnson MK, Kiely DG, et al. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. Am J Respir Crit Care Med 2012;186(8):790-6.

376. Fadah K, Cruz Rodriguez JB, Alkhateeb H, et al. Prognosis in hispanic patient population with pulmonary arterial hypertension: an application of common risk stratification models. Pulm Circ 2023;13(2):e12209.