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CONFERENCE REPORT

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Pulmonary Hypertension Association's 2022 International Conference Scientific Sessions Overview

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Abstract

The considerable progress made in recent years in the diagnosis, risk stratification, and treatment of pulmonary hypertension was highlighted during the most recent edition of the Pulmonary Hypertension Association Scientific Sessions, which was held in Atlanta, Georgia from June 9 to 11, 2022, with the theme: Vision for the PHuture: The Evolving Science and Management of PH. Content presented over the 3-day conference focused on scientific and management updates since the last sessions were held in 2018 and included didactic talks, debates, and roundtable discussions across a broad spectrum of topics related to pulmonary hypertension. This article aims to summarize the key messages from each of the session talks.

KEYWORDS
Clinical Trials as topic, pulmonary hypertension, Pulmonary Hypertension Association, registries

INTRODUCTION

The Pulmonary Hypertension Association Scientific Sessions was held in Atlanta, Georgia from June 9 to 11, 2022. The theme for the conference was Vision for the PHuture: The Evolving Science and Management of PH. The content focused on scientific and management updates since the last sessions were held in 2018 and included didactic talks, debates, and roundtable discussions across a broad spectrum of topics related to pulmonary hypertension. This article aims to summarize the key messages from each of the Sessions talks.

WHAT HAVE WE LEARNED FROM PULMONARY HYPERTENSION ASSOCIATION CONFERENCE 2018?

Update on Clinical Trials, Dr. Corey Ventetuolo

This session focused on emerging therapies for treating pulmonary arterial hypertension (PAH), trials of combination therapies, and new trial designs.

The FREEDOM-EV trial, which is a double-blind, randomized trial, compared oral treprostinil with placebo

when added to single-agent monotherapy, with the primary outcome being clinical worsening. The primary endpoint occurred in 26% of the oral treprostinil arm compared to 36% of the placebo arm with no difference in mortality or progression to parenteral treprostinil.[1]

In the REPLACE trial ($n = 226$), patients on phosphodiesterase type 5 (PDE5) inhibitors (with or without an endothelin receptor antagonist [ERA]) and intermediate-risk and functional Class III were randomized in open-label fashion to continued usual care or to switch to riociguat in place of a PDE5 inhibitor. The primary endpoint was clinical improvement at Week 24, which was met by 41% in the riociguat group versus 20% of the PDE5 inhibitor group (odds ratio [OR]: 2.78; 95% confidence interval [CI]: 1.53–5.06; $p = 0.0007$). This trial suggests that switching to riociguat for patients who are failing PDE5 inhibitors may be a good alternative for some patients.[2]

The TRITON trial was conducted to test the relative efficacy of upfront dual versus triple oral therapy. The trial was a multicenter, double-blind, randomized, Phase III study randomizing 247 patients to either macitentan and tadalafil plus selexipag versus placebo. The primary endpoint was a change in pulmonary vascular resistance (PVR) at 26 weeks. The results showed no difference in the primary endpoints; however, there was a nonsignificant 41% (hazard ratio: 0.59; 95% confidence interval: 0.32–1.09) reduction in disease progression in the upfront triple combination therapy group.[3]

Ongoing nonvasodilator trials

High estradiol and low dehydroepiandrosterone sulfate (DHEAS) in both men and women are associated with worse hemodynamics and shorter 6-min walk distance (6MWD). A small study ($n = 18$) found a modest increase in 6MWD to 26 m in the treatment arm, which has motivated several related, ongoing trials. The EDIPHY trial (NCT03648385) is currently enrolling patients to study the effect of supplemental DHEAS on the primary endpoint of the right ventricular (RV) strain on cardiac magnetic resonance imaging (MRI). The PHANTOM trial (NCT03229499) is a fully enrolled randomized, Phase II trial of anastrozole with a primary endpoint of 6MWD at 1 year. Finally, T3 PAH (NCT03528902) is a single-center, Phase II trial, testing the effect of tamoxifen on a tricuspid annular plane systolic excursion and several secondary clinical outcomes.

Sotatercept is a tumor growth factor-β ligand trap that reduces activin signaling, thereby increasing bone morphogenetic Protein (BMP) signaling, resulting in a less proliferative state. The PULSAR trial randomized patients on background PAH therapy to placebo or two doses of sotatercept with a primary endpoint of change in PVR at 24 weeks. The intervention arms had a significant reduction in PVR.[4] The STELLAR (NCT04576988) trial is Phase III multicenter and fully enrolled with results expected soon.

HOW CAN REGISTRIES IMPROVE THE FUTURE OF PH CARE? DR. NICHOLAS KOLAITIS

PAH registries provide information on survival metrics, outcomes, risk stratification, PAH subgroups, the impact of PAH on quality of life, and the effects of clinical management. Large PAH registries also facilitate the creation of risk calculators and risk stratification tools such as REVEAL, COMPERA, and ERS/ESC. Since 2018, the REVEAL risk score was updated to REVEAL 2.0, which added all-cause hospitalization and renal function to improve risk stratification. REVEAL 2.0 is more accurate than the parent score and is validated for up to 5 years of follow-up.[5] REVEAL Lite 2.0 includes noninvasive data that is more readily available such as functional class, 6MWD, renal function by estimated glomerular filtration rate, brain natriuretic peptide (BNP)/N-terminal prohormone of BNP (NT-proBNP) in addition to systolic blood pressure and heart rate. It was found that the REVEAL Lite 2.0 approximates the REVEAL risk calculator in estimating risk categories for 1-year mortality in a way that is more clinically accessible.[6] COMPERA became more complex by more stratification of the intermediate risk to intermediate low and intermediate high risk, which showed better delineation of risk that was validated in the COMPERA registry and also in the French PHA registry.[7]

Registries also help identify differences among PAH subgroups. For example, PHAR registry investigators noted a high prevalence of methamphetamine-associated PAH in the western United States and that those patients are treated similarly with upfront combination therapy but are less likely to be on triple therapy or parenteral prostacyclin therapy. The PHAR registry also showed high coexistence of illicit drug use among those with human immunodeficiency virus-associated PAH. Finally, patients with portopulmonary hypertension were found to have a lower rate of college education, higher rate of unemployment, and lower income compared to idiopathic PAH.[8–10]

Many registries inform clinicians on how PAH affects the quality of life. The emPHasis-10 instrument is a PH-specific quality-of-life metric that correlates well with

clinical outcomes including 6MWD, BNP, and NT-proBNP, as well as age, education level, body mass index (BMI), and the REVEAL score. Min et al. used PHAR and evaluated the relationship of survival metrics such as emPHasis-10 on quality of life, finding that high-risk scores were consistently associated with worse quality of life.[11]

Registries also revealed the hemodynamics of different PAH subgroups and the effect of different hemodynamics on the progression of the disease. As patients age, there was a decline in PVR, mean pulmonary artery pressure (mPAP), and pulmonary artery systolic and diastolic pressures. Patients at high altitudes were found to have higher oxygen requirements and higher PVR.[12] In the COMPERA registry, PVR was found to have a better prediction of mortality than mPAP.[13]

Registries have also provided insight recently into management practices and effectiveness. The COMPERA registry showed that despite trials like AMBITION, which showed a benefit of combination therapies, still we have room to start more patients on combination therapies.[14] On the other hand, a retrospective trial analyzed data from the French PAH registry. The objective of this trial was to assess the long-term survival of PAH patients based on their initial treatment strategy. In this trial, 1611 patients were included, 984 patients in the monotherapy group, 551 in the dual therapy group, and 76 in the triple therapy group. The triple therapy group had younger members, and more females were in the group when compared to other groups. The survival rate in 5 years was 91% in the triple therapy group and 61% in both the monotherapy and dual therapy groups.[15] Lung transplantation is an option in some patients with advanced disease. The lung allocation score (LAS), which helps in allocating organs in the United States, lacks important clinical parameters in PAH patients, resulting in an underestimation of risk. Chen et al., using United Network for Organ Sharing (UNOS) registry, studied the effect LAS had on lung transplantation for PAH patients. The results showed that PAH patients have a lower cumulative incidence of transplants and a higher cumulative incidence of waitlist death.[16] In 2015 the UNOS added parameters such as cardiac index and bilirubin level, which are thought to help patients with PAH. Kolaitis et al. investigated the effect of this change and PAH patients still have a low incidence of transplants and a high incidence of waitlist death.[17] Finally, in advanced disease, palliative care should be considered, and the PHAR registry showed in unpublished data that only 43% of patients were referred at the last clinic visit before their death.

RECENT BASIC SCIENCE ADVANCE FOR CLINICIANS, DR. KURT PRINS

Since the mortality rate of PAH patients remains high with current therapy targeting common pathways involved in the pathophysiology of PAH, researchers are studying different and novel pathways that could alter the disease course. One novel approach under investigation is the role of epigenetics in PAH. Epigenetics is the modulation of genes and protein expression without modifying the DNA. Bromodomain and extraterminal motif (BET) proteins exert epigenetic modification by binding to histones to induce the transcription of proinflammatory and antiapoptotic factors. In preclinical models, BET inhibitor exposure leads to improved hemodynamics and histopathology.[18] A pilot study of the BET inhibitor apabetalone in humans resulted in a reduction of PVR and increased cardiac output, motivating further human studies.[19]

Cellular senescence is a process where the cell undergoes a terminal stage of growth arrest and becomes very resistant to apoptosis. This occurs in response to endogenous or exogenous stress that includes hypoxia, mitochondrial dysfunction, telomere dysfunction, oncogene activation, and persistent DNA damage. This process can lead to a proinflammatory state via secretory senescence phenotype and through signaling can induce smooth muscle proliferation.[20] Cellular senescence might play a role in PAH pathophysiology. For example, congenital heart disease-related PAH was associated with higher levels of prosenescence markers. Targeting cellular senescence is possible with a class of drugs known as senolytics. After confirming the ability of ABT263 to induce cell death in senescent cells, Van Der Feen et al.[21] demonstrated that treatment with the senolytic ABT263 resulted in significant improvement in hemodynamics and reversal of pulmonary vascular remodeling in a rodent model of PAH due to a left-to-right shunt. In humans, we do not yet know the consequence of long-term senescence modulation.

The microbiome is a complex system that contains bacteria and other organisms such as fungi, viruses, and Archaea. It was reported that PAH patients had altered microbiomes and had distinct gut microbiome systems with enrichment for organisms that secrete trimethylamine N-oxide (TMAO), a metabolite reported to be proinflammatory.[22] Targeting TMAO with 3,3-dimethyl-1-butanol in a rodent model of PAH resulted in a reduction in right ventricle systolic pressure (RVSP).[23] A pilot study is currently recruiting to test intestinal microbiota transplantation (IMT) in PAH patients. This is a Phase I safety and feasibility trial to include 12 patients and follow-up for 6 months with primary endpoint frequency of adverse events and compliance proportion to the IMT (NCT04884971).

IMPACT OF COVID-19 ON PULMONARY VASCULATURE AND PH CARE, DR. JOHN RYAN

Care for patients during the COVID-19 pandemic was significantly disturbed. More than 90% of care was through telemedicine, and around 30% of patients did not see their providers as previously scheduled. Telemedicine requires access to technology such as smartphones, and 26% of US households reported that they do not have access to such technology. Seventy percent of PAH patients who developed COVID-19 were hospitalized, with 30% requiring intensive care and around a 12% mortality rate from COVID-19.

Social determinants of health, such as education level and income, are known to be associated with PAH risk for progression, and those factors were also compromised, which may have led to even worse outcomes in PAH patients. Other health disparities also affected PAH patients during the COVID-19 pandemic. Factors such as race, education level, and language barriers negatively impacted efforts to deliver care to PAH patients remotely. Clinically, it was observed that COVID-19 patients are at high risk of developing pulmonary embolism and chronic thromboembolic pulmonary hypertension (CTEPH), as well as PH that is directly attributable to COVID-19 in the absence of thromboembolic disease. Finally, COVID-19 impacted health care delivery worldwide; our PAH patients suffered from this pandemic due to barriers in receiving health care and due to negative impacts on social factors such as income and education, which are also known to adversely affect their disease severity.

THE FUTURE OF THERAPY FOR PULMONARY HYPERTENSION

New treatments and targets, Dr. Robert Frantz

Mechanical interventions to help in PAH are considered for patients who fail medical therapy and are not candidates for transplant. Atrial septostomy is one possible method, which helps unload the RV at the expense of systemic hypoxemia while maintaining adequate oxygen delivery. Reverse Potts shunt is another method to offload the RV by creating a connection between the pulmonary artery and the aorta. For this to be successful, patients should have PA pressure higher than the systemic pressure to ensure right to left shunt. Recent case series have been published with the creation of a reverse Potts shunt with a radiofrequency catheter that created an opening between the left PA and the descending aorta; no complications were reported, and the functional class was improved; however, longer follow-up is needed.[24]

New treatments for PAH targeting different pathways or a different formula or dosing of drugs that we know are effective in treating PAH might shift the paradigm. Macitentan, an ERA, is known to be effective in PAH. An ongoing trial will examine higher doses of macitentan in addition to ralinepag, a prostacyclin receptor agonist that acts similarly to selexipag but has a longer half-life and higher affinity to the receptor. As discussed previously, sotatercept is another new drug that has been studied in the PAH treatment; it helps rebalance BMPR2 signaling to promote an antiproliferative state. Inhibiting tyrosine kinases is another pathway with possible benefits for patients with PAH. Inhaled seralutinib works by blocking platelet-derived growth factor receptors, colony-stimulating factor 1 receptor, and c-KIT. This drug showed benefit in animal studies, was well tolerated in the Phase I trial, and is now being studied in a fully enrolled Phase II trial in treating PAH patients (NCT04456998). The serotonin pathway is a possible target in PAH treatment. Serotonin promotes pulmonary vascular proliferation and vasoconstriction; reduction of the peripheral serotonin might reverse pulmonary vascular remodeling. Rodatristat, which works on the pathway as a peripheral tryptophan hydroxylase 1 inhibitor, is currently being studied in a Phase II trial that is still enrolling (NCT04712669).

Novel trial designs and endpoints, Dr. Ioana Preston

The scientific community in PAH has evolved rapidly over time in many aspects of how clinical trials are conducted, such as changing composite endpoint targets to better and more feasible endpoints that could provide a meaningful answer to our questions and, instead of studying one drug in advanced disease, studying multiple drugs in less advanced patients. Through trials like AMBITION, RESPITE, and REPLACE, we learned that composite endpoints, which had not been validated previously and were easier to evaluate, such as functional class, lack of clinical worsening, and composite endpoints of betterment, may be a better approach to conducting clinical trials in PAH.[25–27] Risk scores in PAH such as REVEAL and COMPERA can assess prognosis and give an impression about survival; these scores have not yet been used as a composite endpoint in prospective trials but have been applied in post hoc analyses. Using these scores as endpoints in clinical trials might improve the ability of trials to demonstrate meaningful changes in clinical status, although this

approach requires further validation. In terms of available risk scores, REVEAL Lite 2.0 is a more clinically feasible score because it contains modifiable noninvasive parameters, but as with other scores, it lacks RV assessment, which is a crucial survival indicator. Another limitation of REVEAL Lite 2.0 and other validated scores is that they focus on clinical predictors of risk that may be less meaningful to patients and lack the evaluation of patient-centered outcomes such as quality of life, symptom burden, and more specific assessments of daily function outside of basic functional class.

RV function has not been frequently used as an endpoint despite RV failure negatively impacting prognosis in patients with PAH. REPAIR studied patients on macitentan with or without PDE5 inhibitor with improvement in RV function assessed by cardiac MRI as an endpoint. At 26 weeks, there was a clinically significant improvement in RV function and stroke volume.[28] It is also important to remember that, in general, patients care more about how they feel and function than their RV function or hemodynamic measures. New methods to monitor daily physical activity such as actigraphy may enable physical activity to be included as an endpoint in future clinical trials, especially since using devices such as actigraphy to count steps or total energy expenditure has been found to correlate with functional class, 6MWD, and health-related quality of life measures.[29]

The TRACE trial randomized patients to selexipag versus placebo and used accelerometry for 24 weeks to assess the mean difference in activity time and step count, with results that favored the selexipag group, but did not reach statistical significance.[30] Looking into other disease literature, PHYSACTO PROactive study in chronic obstructive pulmonary disease (COPD) used scores that combine patient-reported outcomes with accelerometer-derived data to assess patient physical activity, and these scores are being used as endpoints in the COPD literature. In this trial, there was a 20% improvement by just using accelerometry in the placebo and behavioral treatment groups. However, using accelerometry might have high variability due to weather and behavior, and we must consider these variables when designing studies using actigraphy-based endpoints.[31]

AI, network medicine, and systems pharmacology, Dr. Jane Leopold

Artificial intelligence (AI) is intelligence exhibited by machines mimicking human cognitive intelligence, such as learning and problem-solving. In the medical field, AI was found to predict race from medical imaging.[32] In the field of pulmonary vascular disease, AI was found to predict patients at risk of idiopathic PAH. A trial's investigators input information about patients and AI predicted those at risk based on factors such as age, specialty of the physician following the patient, and prevalence of the PAH in the group that is being studied.[33] The AI-based model predicted outcomes in PAH patients better than REVEAL 2.0, but AI-based risk assessment remains imperfect and further work is needed to determine how best to integrate with clinical risk assessments.

Network medicine is based on the hypothesis that human disease is a consequence of the perturbation of a biological network from either genetics, proteins, metabolic derangements, or exposures on a cellular or organ level. Network topology can be used to identify interactions between various proteins and or genes that might have biological meaning. Using algorithms, we can define a function or disease module from these connections. These analyses using networks have the advantage of clustering patients with similar features since most people with similar diseases have different characteristics. In PAH, networks can also help identify various disease mediators as well as different predictors of outcomes in PAH patients to help improve risk stratification. Networks also help in seeing patients with common phenotypes, grouping patients with similar phenotypes, and then, based on the literature, deciding on what medications work on patients with the phenotype to allow for more targeted therapy.[34]

Repurposing drugs based on the interaction of drugs with genes was also studied using networks. For example, hydroxychloroquine is used to treat rheumatoid arthritis and this method showed other benefits of this drug, such as preventing coronary artery disease (CAD).[35] In PAH also, there were some predicted interactions between existing drugs and genes that have been linked with disease, although this requires further validation to determine whether repurposing these drugs for PAH would be practical and to determine the subsets of patients who would be expected to benefit from these therapies.

In summary, future research requires AI, which can be helpful but needs accuracy and reproducibility. Systems pharmacology for drug repurposing has excellent potential for new therapeutics in different conditions; however, not without challenges such as patent considerations, regulatory issues, and organizational hurdles.

Initial treatment strategies: Debate on the role of upfront triple combination therapy: Dr. Harrison Farber and Dr. R. James White; moderated by Dr. Hillary DuBrock

The role of dual versus triple combination therapy in PAH was discussed in a debate format by Dr. Farber and Dr. White. The CON side took the role of arguing against upfront triple combination therapy due to a lack of randomized clinical trials (RCTs) demonstrating the clinical benefits of this strategy. Data supporting the clinical benefits of upfront triple combination therapy has thus far come from observation trials without randomization or matched control groups limiting the ability to determine the true benefit of upfront triple therapy compared to dual combination therapy.[15,36–38] Further, the TRITON study did not demonstrate a significant benefit with selexipag when used in combination with oral combination therapy in newly diagnosed PAH.[3] Further, combination oral therapy with an ERA and PDE-5 inhibitor has been sufficient to generate significant hemodynamic and functional improvements in the AMBITION trial.[25]

The PRO side argued that early use of parenteral prostacyclin therapy in some intermediate- and most high-risk patients could improve outcomes of interest with tolerable side effect profiles. There was agreement that initial triple therapy is not necessary for all PAH patients and would lead to unnecessary costs and side effects if not appropriately targeted. He emphasized that RV function is modifiable by therapies to lower PVR and that posttreatment changes in RV function have been shown to be an important marker of outcomes in PAH.[39–41] He emphasized that, although data from trials mentioned by the CON side are not randomized, the improvements in hemodynamics and echocardiographic parameters seen with upfront triple therapy compare favorably to historical controls and expected outcomes for patients with high-risk PAH.[36,38] He also emphasized that early data from parenteral prostacyclin showed that dramatic reductions in PVR are possible with these therapies,[42,43] and that while many patients do have a response to upfront dual, oral combination therapy, recent observational data demonstrated that many patients are unable to reach treatment targets on oral therapy alone.[44] Taken together, the PRO argument suggests that early assessment of patient response to dual therapies is necessary and that escalation to triple therapy with parenteral prostacyclin should be considered for patients who have not improved or reached treatment goals per risk stratification.

The discussion also emphasized the benefits of a balanced approach to therapies that emphasized additional treatment strategies such as diuretics, supplemental oxygen as needed, physical therapy, nutritional counseling and support, and management of medication-related side effects, as well as the incorporation of patient preferences and quality of life.

PH THROUGHOUT THE LIFECYCLE, ADOLESCENT ISSUES IN PH: PANEL DISCUSSION

Dr. Jessica Badlam, Erin Ely, BSN, RN, CPN, Alvin Rocha, MSN, RN, CPN, and Dr. Nidhy Varghese

There is little guidance for the successful transition of young adults with pulmonary hypertension (PH) to adult centers leaving the patient, caregivers, and teams unprepared and at risk for negative outcomes. This panel suggested that the discussion of transition should start at 12–13 years, including parents as well as the child. Challenges that require vigilance and attention include watching for early developmental milestones, changing liquid medications to pills, learning independent pump management, and addressing school challenges.

Specific examples of transition preparation were discussed: including suggestions to focus on helping patients ages 12–14 years understand their history and medications, and working with patients ages 14–16 years to be able to discuss their disease in more detail at every visit with teaching prompts. For teenagers 16–18 years, the panel suggested shifting focus to exploring the future including college or adult plans and starting to role-play adult center visits regarding repeating their health history and medications. The 18th birthday brings upon changes in legality and presumed adult responsibility as patients rely less on the parents and it may be hard for parents to transition away from calls and appointment scheduling. From 18 to 21 years, considerations include setting up visits for transition with the adult team and ideally combined meetings to ease patients and parents through the transition to adult medicine. Communication between the pediatric and adult teams is beneficial; remembering that pediatric centers are less common than adult centers and there may not be close relationships with adult centers near the patients' homes.

Empowering young patients to take control of their own care is important in this process. Change can be hard, especially as these patients are familiar with the long-term, consistent care at pediatric centers. This transition to adulthood has practical and legal implications that cannot be ignored. Insurance and pharmacy

changes cause added vulnerabilities, and financial counselors and social workers are important to include in the transition stages.

Education on the importance of medications is critical during transition stages, as changes in the living environment, such as leaving their childhood home, may challenge adherence. Suggestions included creating support systems and utilizing peer relationships such as networking locally and within the Pulmonary Hypertension Association. Transition at the time of high school graduation is often not ideal as there are already many changes in a child's life. Access to counseling is important, and adult centers should encourage being proactive in maintaining mental health.

Lastly, contraceptive management was addressed, as these discussions and therapies start in pediatric programs. It is common to use pediatric gynecologic expertise with pubertal changes and important for the PH pediatrician to have these difficult conversations at vulnerable ages, as discussions about reproductive health will continue throughout the lifespan. A variety of oral, implanted, and injected menstrual suppression and regulation methods are utilized in the pediatric setting including intrauterine devices (IUDs). If appropriate, consider combining IUD insertion with an anesthesia event, like cardiac catheterization, if possible. These sensitive conversations with young girls and their parents can be particularly challenging, using terminology including “REMS mandates” and “decreasing blood loss” can be techniques to overcome these barriers.

The panel concluded with a request for communication between adult and pediatric colleagues and welcome opportunities to partner in successful pediatric-to-adult patient transitions.

TELEMEDICINE TOOLS: WHAT ARE THEY AND HOW TO BEST UTILIZE THEM FOR PAH PATIENTS

Dr. Lana Melendres-Groves

Telehealth is an umbrella term for the use of electronic information and telecommunication technologies to support and promote long-distance clinical care. Telehealth includes telemedicine, the use of smart devices, remote monitoring, medication reminders, video conferencing, AI, and so on.[45]

Before COVID-19 pandemic, telemedicine was already experiencing a significant trend upward, although this did not compare to the massive increase in telemedicine uptake seen during the pandemic in 2020. In February 2020 to April 2020 primary care telemedicine visits moved from <1% to nearly 43%, and now between 60% and 90% of physicians are using telemedicine services to some extent. The ACCP PVD Network steering committee found that 93% of patient care was affected and telemedicine use increased from 15% prepandemic to 84% during the early pandemic.[46]

The benefits of telemedicine include increased frequency of monitoring, decreased emergency room visits, reduced hospitalizations, decreased financial costs related to travel, and insight into patients' living environments and surroundings.[47] Limitations include clinician scarcity, legal complexity, and licensure challenges beyond state lines. Limited physical exam abilities may also decrease a sense of patient connection. Lastly, there remains a disparity in health care and access to technologies in already vulnerable populations.[48,49]

In summary, telemedicine offers the ability for widespread delivery of high-quality care including increased access to comprehensive and regional care centers. However, as a community we need better metrics to assess the impact of telehealth on patient care, systems to aid in providing seamless virtual care to all demographics including the most vulnerable, and technological solutions to create equity as telemedicine changes the face of patient care.

DEBATE: POTTS SHUNTS VERSUS LUNG TRANSPLANT

Dr. Erika Berman Rosenzweig, Dr. R. Mark Grady, and Dr. Ernestina Melicoff Portillo

This session was presented with four cases and expert discussion with audience participation. Although lung transplantation has been accepted as one of the only end-stage interventions for PH, reverse Potts shunt has gained recognition as another intervention. A classic Potts shunt was described as a left-to-right shunt connecting the left pulmonary artery (PA) to the descending aorta and is typically used for cyanotic infants. In 2004, the reverse Potts shunt showed success shunting from the pulmonary artery to descending aorta to treat severe suprasystemic right heart pressures. This causes differential cyanosis providing nearly fully saturated blood to the upper body and coronary arteries with lower saturation in the lower extremities where it is generally well tolerated. The discussion primarily referenced Dr. Grady's finding published in the Journal of the American College of Cardiology in 2021.[50]

Case 1 described a function Class II child with a BMPR2 mutation and RV dysfunction who had been medically optimized on triple combination therapy including parenteral prostacyclin. A consideration of reverse Potts shunt is made but would require measurement of exertional PA pressures to ensure suprasystemic pressure and that the child would benefit from a valve shunt. The placement could have the potential to reduce the burden of therapy in this active child as 2/3rd of children followed with reverse Potts shunt were able to come off pump therapy.[50] However, the panel would recommend a meeting with the transplant surgery team in case of decompensation. It is possible that a shunt could be considered as a bridge to transplant, but these evaluations should occur simultaneously, especially with current lung allocation challenges in the United States.

Case 2 described a 14-year-old with idiopathic PAH requiring epinephrine and vasopressin in the intensive care unit presenting recurrent near syncope. The first goal is to evaluate for medication optimization and other acute and treatable diseases. This child was quite ill and concern exists that if the RV is too burnt out it may not generate suprasystemic pressures but could consider septostomy as mortality may be worse with a shunt. Conversation noted that patients on extracorporeal membrane oxygenation (ECMO) with a bridge to Potts shunt for heart failure did poorly and cited one out of 11 patients on ECMO with Potts shunt left the hospital alive.[50] This case stresses the importance of multidisciplinary team planning.

Case 3 described an 18-year-old with DLCO of 48% and worsening hypoxemia with suprasystemic RV pressures. It was concluded that evidence supported chronic hypoxic lung disease and would not be an appropriate candidate for reverse Potts shunt and more favorable for a lung transplant. Discussion included added risk of complicated transplant with prior thoracotomy, thus the use of shunts as a bridge to transplant should be carefully considered.

Case 4 described a 43-year-old with scleroderma on inhaled treprostinil with suprasystemic PA pressures on the last heart catheterization. Medical optimization is the first priority and Potts shunt could be considered if the patient is not a lung transplant candidate, although data are primarily in children. The discussion also addressed the outcomes of lung transplant for ages 15–23 are worse than other groups, and with considerations, it is promising that reverse Potts shunt could be considered for bridging as 5-year survival was 68% after surviving the initial procedure.[50] The answers are not straightforward. Talking with a transplant team early is helpful, especially with planning for atrial septostomy or reverse Potts shunt, which has the promise of becoming a more common viable end-stage therapeutic option.

PHA/PVRI JOINT SESSION: THE GLOBAL BURDEN OF PH: BEYOND GROUP 1

A global perspective on PH, Dr. Werner Seeger

The GoDeep project was founded in 2018 under the umbrella of the Pulmonary Vascular Research Institute (PVRI) by three founding members, Imperial College London (UK), Johns Hopkins Hospital (USA), and Justus-Liebig University Gießen (Germany), to compile data on patients with PH worldwide as a central meta-registry.[51] Data from local PH registries is processed via an automated process that results in parameter translation and harmonization, data deidentification, and encrypted transfer of deidentified data to the GoDeep meta-registry.

Currently, 350 phenotypic parameters (divided into priority categories: mandatory, essential, recommended, and extended) are collected as part of the meta-registry. There are currently 14 centers in Europe, North America, and South America participating in GoDeep with another 14 centers in ongoing negotiations. This has resulted in the enrollment of 14,000 subjects with PH and 1735 comparators and over 1.9 million data points.

Initial data have demonstrated that American subjects enrolled tend to be younger and to have a higher proportion of PAH compared to European enrollees. Subjects enrolled in the meta-registry have been followed for an average of about 3 years, but there is a subset of subjects who have been followed for more than 10 or 20 years, which may allow for inquiry into predictors of longevity in PH.

Use and access rules allow for permanent access to basic and detailed data for GoDeep consortium members, while academic-based PVRI members can access basic data after requesting authorization. For PVRI members, access to detailed data requires application and payment of an access fee. Industry and external academic organizations are required to complete an application process and pay an access fee for any level of data access. Data use agreements allow for the export of analysis results to nonconsortium members, but not the sharing of raw data.

Moving forward, the GoDeep meta-registry aims to expand to allow global participation from all tiers of centers and clinical practice settings by setting the threshold for participation at an appropriate level to balance maintaining data quality with maximizing participation. In particular, the registry is interested in expanding to African and Asian centers to better be able to capture the worldwide spectrum of PH phenotypes. In

this aim, GoDeep will support the creation of new center-based registries by providing state-of-the-art REDCap PH registry templates and onsite hosting without licensing fees. The registry also aims to dynamically determine which data should be prospectively collected over time and to be able to adjust as there are changes in the types of data available (such as increasing use of cardiac MRI or -omic techniques). For example, there is currently ongoing discussion of possibly including pseudonymized data for a subset of patients to allow incorporation with blood and genetic data collected as part of PAH ICON.

Ultimately, the GoDeep meta-registry aims to help PH investigators answer important epidemiological questions about the various groups and subgroups of PH by compiling high-quality data from centers around the world with the goal of offering insights that improve PH-care worldwide.

Group III PH with ILD: Diagnosis and management, Dr. Namita Sood

PH is a common complication of interstitial lung disease (ILD) with prevalence rates varying by types and severity of ILD, with the highest frequencies seen for patients with end-stage idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE), and sarcoidosis.

PH, even to mild degrees, has been shown to be a significant risk factor for mortality in patients with ILD.[52] Degree of restriction does not seem to predict the development of PH, as mean PA pressures do not correlate with forced vital capacity measurements,[53,54] and the ARTEMIS-IPF trial demonstrated that a relatively high proportion of patients with even early IPF can have PH.[55]

PH is often a complex process in patients with ILD as development can be related to vasculopathy from cytokine and immune dysregulation, acute and/or chronic pulmonary emboli, or parenchymal destruction leading to hypoxic vasoconstriction, decreased vascular compliance, and obliteration of the vascular bed, often with contribution from comorbidities such as obstructive sleep apnea (OSA), CAD, and left ventricular (LV) diastolic dysfunction, which are all common in this patient population.

This complexity impacts treatment strategies, as nonselective pulmonary vasodilator therapies can lead to worsening ventilation–perfusion (V/Q) mismatch and worsening hypoxemia.[56] This concern has led to exclusion of patients with ILD from most clinical trials of PAH-specific medications. Of the trials that have been completed with systemic pulmonary vasodilators in ILD patients, none have shown significant clinical benefit,[57] and several have been stopped early due to evidence of harm.

Inhaled treprostinil therapy was recently tested in subjects with PH related to ILD in the INCREASE trial.[58] This trial was conducted in a mixed population of ILD patients with moderate PH at baseline, with the majority having IPF, CTD-ILD, chronic HP, or CPFE. Treatment with inhaled treprostinil resulted in an increase of 6MWD by about 30 m compared to controls and a significant decrease in NT-proBNP over a 16-week period. Subgroup analyses indicated that the greatest benefit was seen in subjects with PVR > 4 WU and those able to tolerate a higher number of breaths (≥12). The results of this trial led to the Federal Drug Administration (FDA) approval of inhaled treprostinil for PH related to ILD in 2021.

Given the complexity of care, a multidisciplinary team comprised of physicians with expertise in ILD, PH, rheumatology, radiology, and pathology, as well as nurses, respiratory therapists, and pharmacists with expertise in working with these conditions is beneficial in caring for these patients. Management of these patients should center around addressing the underlying lung disease and treating reversible causes if possible, optimizing comorbidities such as OSA and diastolic heart failure, and preventing hypoxemia with supplemental oxygen as necessary. PH should be suspected when there is worsening dyspnea out of proportion to PFTs, increasing oxygen requirements, rapid desaturation with mild activity, significant reductions in DLCO, reductions of functional capacity as evidenced by a low 6WMD, or clinical evidence of RV failure on exam. While an echocardiogram often serves as the initial screening test for PH, estimates of RVSP do not always correlate with mPAP on right heart catheterization and can lead to but under- and overestimations of PH.[59] Other proposed screening tools for PH in this population include PA size on chest CT, measurements of DLCO on PFTs, or BNP/NT-proBNP but each of these is limited in their diagnostic accuracy or needs further validation. Overall, there is a high likelihood of PH if TR jet velocity on TTE is >3.4 m/s, NT-proBNP is elevated, and/or DLCO < 42%, although a right heart catheterization (RHC) is necessary to confirm a diagnosis of PH. Given the high risk of mortality in patients with ILD-related PH, referral for transplant evaluation should be considered in patients at the time of PH diagnosis.

VTE is also more frequent in patients with IPF and may contribute to concurrent CTEPH. Traditional V/Q scan does not perform well in this population due to parenchymal abnormalities, but a small study showed single-photon emission computed tomography (CT)/V/

Q was highly sensitive and specific compared to CT pulmonary angiography.[60]

Future work should focus on better phenotyping and characterizing patients to identify which patients are most likely to benefit from treatment, potentially through the use of biomarkers and proteomic and genomic data. Exploring common pathways between the pathogenesis of parenchymal and vascular remodeling may also allow for novel drug targets that target both processes. Further work is also needed to define and standardize acceptable clinical and research outcomes of interest in this population from potential options including risk stratification tools, quality of life measures, functional assessments, or imaging changes.

In summary, PH related to ILD remains a complex condition requiring multidisciplinary care. While the results of inhaled treprostinil in ILD-related PH are promising, further work is needed to define patients most likely to respond to treatment and to identify novel treatment targets to change the course of disease in this highly morbid condition.

THE NEW NORMAL: IMPACT OF THE NEW HEMODYNAMIC CRITERIA ON DIAGNOSIS AND TREATMENT OF PULMONARY HYPERTENSION, DR. STEVEN MATHAI

The diagnostic criteria for PH were changed at the Sixth World Symposium on Pulmonary Hypertension in 2018 to a mean pulmonary artery pressure (mPAP) >20 mmHg.[61] PH is further divided into precapillary, postcapillary, and combined pre- and postcapillary PH based on the PVR above or below 3 WU and pulmonary artery wedge pressure (PAWP) above or below 15 mmHg.

This change was made in part due to evidence demonstrating that mild elevations in mPAP of 20–25 mmHg are associated with an increased risk of mortality.[62–64] In scleroderma, a mildly elevated mPAP (21–24 mmHg) is also associated with a significantly increased risk of progression to PAH compared to those patients with normal mPAP ≤ 20 mmHg.[65]

There is limited data available at this time on how the new definition of PH has impacted the prevalence of PH in various etiologies worldwide. In a study of a scleroderma population, the new definition resulted in the reclassification of 7 out of 268 patients to a diagnosis of PH (1 PAH, 3 with Group 3 PH, 3 postcapillary PH). Of note, 76 of the 268 patients had elevations of mPAP > 20 mmHg but did not meet the criteria for any category of PH due to PVR < 3 WU and PAWP < 15 mmHg.[66] It remains unclear what to do with these "unclassifiable" patients. TR jet velocity > 2.7 m/s appears to be the best echocardiographic threshold for the new PH definition with a sensitivity of 80% and specificity of 66%.[67] In addition, a TR jet velocity > 2.7 m/s is more likely to be associated with PH if RA or RV enlargement is also present.

Different algorithms and strategies have been developed to detect early PH in at-risk cohorts. For example, the DETECT algorithm was developed in patients with scleroderma with at least 3 years of non-Raynaud's symptoms and DLCO < 60% predicted to identify clinical characteristics that should prompt referral for echocardiography, and then echo characteristics that should prompt referral for RHC.[68] This protocol has a 96% sensitivity for identifying patients with PH and seemed to detect patients with earlier stage disease based on functional class. When the algorithm is extended to all patients with scleroderma >3 years duration regardless of DLCO value, the sensitivity is maintained, although the specificity is decreased to 29%.[69]

There are currently limited data or guidelines on appropriate treatment strategies for patients who fall in this new category of PH. The EDITA study[70] demonstrates no difference in mPAP after randomization to 5–10 mg/day of ambrisentan or placebo in patients with scleroderma and mPAP 21–24 mmHg or exercise mPAP > 30 mmHg. However, prior data have shown that treatment with combination therapy with ambrisentan and tadalafil can improve PVR and RVEF over 36 weeks in subjects with relatively mild systemic sclerosis-pulmonary arterial hypertension based on PVR < 4.5 WU.[71] The SEPVADIS study is currently ongoing to study the effects of sildenafil on 6MWD, RV function, and quality of life over a 1-year period in a population of patients with scleroderma and early PVD.

In summary, changes to the hemodynamic definitions of PH were made in response to emerging data on the risks associated with mPAP > 20 mmHg. The new definition seems to have small effects on disease prevalence but will significantly impact screening and early detection algorithms. Despite changes to the hemodynamic definitions, optimal management strategies for patients who fulfill the new hemodynamic criteria for PH are not clear, and there are no approved medications for these patients. Further work is necessary to address this important knowledge gap.

GROUP II PH: ARE WE MAKING PROGRESS? DR. THENAPPAN THENAPPAN

Based on the Sixth WSPH, Group 2 PH—or pulmonary venous hypertension—is defined as mPAP > 20 mmHg with PAWP > 15 mmHg, indicating elevated left-sided

filling pressures. Group 2 PH is the most common type of PH, making up about 2/3rd of prevalent cases with evidence of increasing incidence.[72,73]

Group 2 PH can result from elevations in LV filling pressures due to LV systolic or diastolic dysfunction, mitral valve disease, or left atrial dysfunction/stiffness,[74] which can all contribute to elevations of PAWP.[75] Cases of Group 2 PH can be further phenotyped to isolated postcapillary or combined pre- and postcapillary (Cpc-PH) based on whether the PVR is elevated to >3 WU, indicating the presence of concurrent vascular remodeling. Diastolic pulmonary gradient (PA diastolic pressure —PAWP) is also a surrogate for pulmonary vascular remodeling and is elevated in Cpc-PH.[76]

Patients with PH due to heart failure often undergo global pulmonary vascular remodeling in arteries, veins, and intermediate vessels that correlates with hemodynamic measures.[77] However, it is not well established which patients will develop Cpc-PH, but it is hypothesized that a "second hit" such as genetic and environmental risk factors or comorbidities such as OSA, lung disease, and chronic kidney disease are necessary to drive pulmonary vasoconstriction and remodeling.[75] This hypothesis is supported by the finding that Cpc-PH shares molecular and genetic similarities to PAH.[78] Cpc-PH is also associated with RV/PA uncoupling, which is associated with RV failure and the severity of symptoms.[79]

This also results in abnormal exercise physiology in Cpc-PH with further elevations in PAWP and lower CO compared to isolated pc-PH.[80] These hemodynamic changes have prognostic implications, as PH-LHD is associated with increased mortality and heart failure hospitalization.[81]

Given the prognostic and treatment implications of a diagnosis of Group 2 PH, it is important to correctly identify patients at risk due to specific left heart phenotypes, to accurately determine the probability of PH-HFpEF noninvasively using clinical measures and echocardiographic findings, and to confirm the diagnosis hemodynamically through RHC with accurate measurements of PAWP and use of provocative testing such as exercise and/or fluid challenge when needed. An increase of PVR to >3 WU or PCWP/CO slope >2 mmHg/L on exercise testing or PCWP > 18 mmHg after 500 ml saline bolus over 5–10 min are suggestive of PH related to heart failure with preserved ejection fraction (HFpEF), although more work is needed to validate and optimize these measures.

Unfortunately, current PAH-specific therapies do not work in Group 2 PH and are potentially harmful.[82,83] There is emerging evidence that SGLT2 inhibitors, a modulator of sodium-glucose transporters in the kidneys initially developed for the treatment of diabetes mellitus, may be helpful in treating this condition as they have been shown to improve cardiovascular outcomes in HFpEF[84] and to ameliorate PVD in preclinical HFpEF models.[85] Another potential promising treatment is levosimendan, an ionodilator that functions as a Ca sensitizer and KATP channel activator and is approved for the treatment of HF with reduced EF (HFrEF) in many other countries that have recently been shown to reduce PCWP and increase exercise capacity with no significant increases in adverse events in the HELP study, a Phase II trial of patients with PH-HFpEF.[86]

In conclusion, significant advances have been made in the understanding of the epidemiology, pathobiology, and, recently, the treatment of PH-LHD, but several large knowledge gaps still exist and further work is needed to address these.

CTEPH: UPDATES ON DIAGNOSIS AND MANAGEMENT, DR. NICK KIM

CTEPH, or Group 4 PH, is a disease in which chronic venous thromboembolism (VTE) obstructs pulmonary blood flow resulting in elevated PA pressures. There remain diagnostic challenges in identifying CTEPH and key messages need to be tailored to target audiences. For example, primary care providers should be aware that CTEPH is in the differential for chronic dyspnea or anticoagulation failure. Community cardiologists, pulmonologists, and radiologists should be aware that CTPA is not adequate to rule out CTEPH and that V/Q scan is often required to make the diagnosis. Emergency department physicians should be aware of the different presentations of acute versus chronic PE and the possibility of in situ clot formation in chronic disease. For PH specialists, it is important to recognize the need for referral to a CTEPH center capable of performing pulmonary endarterectomy (PEA) when cases of CTEPH are identified.

It is also important to remember that absence of VTE history does not rule out CTEPH as up to 30% of patients have no prior diagnosis of a pulmonary embolism at the time of CTEPH diagnosis. CTEPH diagnosis may be underdiagnosed as many patients diagnosed with PAH have never undergone V/Q scan[87] and V/Q scans have been shown to have improved sensitivity compared to CTPA in diagnosing CTEPH.[88] It is also important to remember that not all pulmonary artery clots are embolic. PAH patients can occasionally develop in situ thrombosis in the pulmonary arteries, possibly related to endothelial injury.

Results of the V/Q scan need to be interpreted in the context of underlying parenchymal abnormalities for patients with underlying lung disease. Abnormalities on V/Q are more likely to be CTEPH if they are basilar and if the patient has a history of deep vein thrombosis.

The current diagnostic algorithm recommends using echocardiography and V/Q scan as screening tools when CTEPH is suspected, to confirm the diagnosis with RHC and pulmonary angiography, and to utilize hemodynamic and clinical factors, as well as comorbidities to assess risk once CTEPH is diagnosed.[89]

CTEPH treatment can involve surgical treatment with PEA, mechanical treatment with balloon pulmonary angioplasty (BPA), or targeted medical therapy. Many patients receive a combination of these therapies.[90] Treatment decisions should be made in conjunction with a multidisciplinary team with expertise in CTEPH including surgeons, PH clinicians, BPA interventionalists, and radiologists.[90]

Medical therapy can be utilized to lower PVR in subjects with inoperable CTEPH or with persistent PH following PEA. Multiple therapies have been tested in the context of inoperable or persistent CTEPH, and these trials are summarized in Table 1. The AIR study[91] was the first randomized controlled trial (RCT) of medical therapy that allowed for the inclusion of inoperable CTEPH in addition to other forms of PAH and suggested that there may be some benefit to inhaled iloprost. The BENEFiT trial[92] demonstrated improvement in hemodynamics with bosentan in inoperable CTEPH or persistent/recurrent PH after PEA but no change in 6MWD at 16 weeks. This was followed by the CHEST-1 study,[93] which showed improvement in 6MWD and hemodynamics with riociguat in inoperable and post-PEA CTEPH, resulting in the FDA approval of riociguat for treatment of this condition. The Phase II trial MERIT-1 showed that combination therapy with macitentan may add additional benefit to PDE-5 inhibitor therapy.[94] The CTREPH trial[95] also demonstrated significant improvement in 6MWD with high-dose subcutaneous treprostinil in inoperable CTEPH. Selexipag has also been shown to reduce PVR in patients with CTEPH in a small RCT, leading to its approval for this condition in Japan[96]; however, a larger study—the SELECT study (NCT03689244) was stopped early due to futility so utility in this condition is unclear.

Ongoing work is continuing to identify optimal treatment strategies for patients with inoperable or persistent CTEPH. The MACiTEPH trial (NCT04271475) is ongoing to evaluate the benefit of higher dose macitentan in inoperable or persistent CTEPH on 6MWD and time to clinical worsening. The RACE study compared riociguat to BPA in inoperable CTEPH and demonstrated decreased complications for BPA for subjects who had been on prior medical therapy and suggests that upfront medical therapy may be beneficial in patients with inoperable disease.[97] The IMPACT-CTEPH trial (NCT04780932) is also now underway to evaluate the effect of combination oral therapy with macitentan and riociguat compared with riociguat monotherapy before BPA in patients with inoperable CTEPH.

In conclusion, CTEPH is important to diagnose accurately given the potential for surgical and mechanical treatments which can significantly impact patient outcomes. Medical therapy has a role in the management of inoperable or persistent CTEPH. While there is the most conclusive data for riociguat in this population, there is emerging evidence of the benefit of ERAs and prostanoids in this condition. Further work is needed to better define optimal treatment strategies for patients with this condition.

MECHANICAL TREATMENT OF CTEPH, DR. IRENE LANG

CTEPH can affect various levels of pulmonary circulation from the main pulmonary arteries to more distal targets such as subsegmental pulmonary arteries. Mechanical treatments such as PEA and BPA are typically more effective for the proximal disease. The current treatment algorithm relies on pulmonary angiography to make an accurate diagnosis and to clearly establish the pattern of disease. Given the complexity of these cases, the multidisciplinary discussion is crucial to identify the optimal treatment approach. It is also important to incorporate patient-specific factors into the discussion, as the presence of certain risk factors can significantly affect outcomes. PEA remains the treatment of choice when feasible, and outcomes are excellent in appropriately selected patients treated at expert CTEPH centers, while BPA can be considered for patients with CTEPH with more distal (i.e., lobar, segmental, and subsegmental) disease. The optimal approach for patients with the intermediate disease is less clear, prompting the GO-CTEPH trial (NCT05110066), an RCT of PEA versus BPA in CTEPH patients eligible for both treatments.

BPA is often performed as a staged procedure with incremental lesion dilation, as smaller balloon size relative to vessel size helps to decrease the risk of complications such as pulmonary or vascular injury. Most patients require multiple sessions (sometimes up to 20) to receive complete treatment.

There have been significant improvements in BPA outcomes since the first case series was published in 2001, demonstrating a 61% rate of pulmonary injury.[98] Current complication rates for BPA at expert centers

TABLE 1 Multicenter randomized controlled trials of medications in CTEPH

Study	Source	Participants	Population	Intervention	Control	Primary outcome	Main results
AIR	Olscewski et al.[91]	203 (57 with CTEPH)	Severe PAH or CTEPH	Inhaled iloprost—12 weeks	Placebo	Improvement in NYHA Class and 6MWD	Clinical improvement in 16.8% in intervention versus 4.9% in controls ($p = 0.007$)
BENEFiT	Jais et al.[92]	157	Inoperable CTEPH or persistent/recurrent PH after PEA	Bosentan—16 weeks	Placebo	Improvement in PVR/improvement in 6MWD	Bosentan decreased PVR 24.1% from baseline (95% CI: −31.5% to −16.0%, $p < 0.0001$); no change in 6MWD
CHEST-1	Ghofrani et al.[93]	261	Inoperable CTEPH or persistent/recurrent PH after PEA	Riociguat—16 weeks	Placebo	Change in 6MWD	Riociguat improved 6MWD by 46 m compared to placebo (95% CI: 25–67 m, $p < 0.001$), the treatment also resulted in significant improvements in PVR, NT-proBNP, and WHO FC
MERIT-1	Ghofrani et al.[94]	80	Inoperable CTEPH	Macitentan—24 weeks	Placebo	Change in PVR	Macitentan resulted in significant improvement in PVR (73% of baseline vs. 87.2% of baseline with placebo, $p = 0.041$)
CTREPH	Sadushi-Kolici et al.[95]	105	Inoperable CTEPH or persistent/recurrent PH after PEA	Subcut. treprostinil (high dose)—24 weeks	Subcut. Treprostinil (low dose)	Change in 6MWD	High-dose subcutaneous treprostinil improved 6MWD by 40.69 m (95% CI: 15.86–65.53) compared to low dose ($p = 0.0016$)
RACE	Jais et al.[97]	105	Newly diagnosed, inoperable CTEPH	Initial riociguat—26 weeks	Initial BPA	Change in PVR	BPA resulted in a lower PVR at week 26 (39.9% baseline vs. 66.7% with riociguat, $p < 0.0001$); no difference in PVR at week 52. Incidence of BPA-related serious adverse events was lower in patients pretreated with riociguat (14% vs. 42%)

Abbreviations: 6MWD, 6-min walk distance; CTEPH, chronic thromboembolic pulmonary hypertension; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

suggest a 2.5%–15% rate of pulmonary injury.[99,100] Complication rates seem to be impacted by the types of lesions present.[101] Ring-like stenoses and vascular webs are best treated with BPA, while tortuous lesions are thought to have high rates of complications and should likely be avoided. There is also evidence that complications are more likely when treating patients with more severe hemodynamic abnormalities, and the RACE trial suggests that upfront medical therapy to improve hemodynamics can decrease complication rates, as rates of BPA-related serious adverse events were lower in patients pretreated with riociguat (14% vs. 42%) with a similar reduction in PVR at 52 weeks between the two groups.[97] Provider experience matters in both BPA and CTEPH, with data suggesting lower complication rates as clinician experience increases.[102]

The benefits of BPA can often exceed that of medical therapy with a reduction in PVR by about 40% and mPAP by about 30%.[100] Treatment response to BPA is correlated with the number of lesions able to be treated. There is also emerging evidence that BPA can be used to treat residual, distal disease after PEA.[103]

In summary, CTEPH is caused by mechanical obstructions of the pulmonary arteries and can often be treated by mechanical means with either PEA or BPA with excellent results. Decisions about the appropriate treatment strategies are best made by multidisciplinary discussions at expert clinical centers with expertise in both treatments. While PEA remains the treatment of choice for proximal disease in operative candidates, BPA can demonstrate significant hemodynamic benefits in patients with an intermediate or more distal disease with a favorable complication rate when performed by expert clinical centers. Further work is needed to optimize patient selection and treatment approach, and an international BPA registry has been developed to prospectively collect data on BPA cases to aid in this process.

BEYOND VASODILATORS-NONMEDICAL INTERVENTIONS FOR PH: ROLE OF EXERCISE, ACTIVITY TRACKING, AND REMOTE MONITORING IN PH CARE, DR. MARY BETH BROWN

Training the RV and left ventricle (LV) is not the same. Healthy rat models have shown greater metabolic remodeling of the RV including the increased mitochondrial ability to produce ATP and the increased antioxidant capacity after 1 year of exercise training. Structural remodeling of the RV was reversible and dose-dependent with the intensity of the exercise.[104–106] More research is available with animal models because exercise is difficult to model in humans. Therefore, there is a lot we do not know about exercise despite a Grade 1a recommendation for exercise in PAH, and we need to know how to assess and individually prescribe exercise.

The optimal approach to exercise training in PH to achieve benefit without the detriment of maladaptive RV remodeling is unknown.[107] Hitting an exercise benefit threshold without being detrimental is important to understand and then translate into exercise prescriptions. For example, high-intensity interval training (HIIT) for rat models with mild PH reversed RV hypertrophy but not with continuous training and it is unclear how this translates to different disease severity and etiology.[108] Interestingly, in a follow-up study with a manuscript in progress, in a rat model of severe PH, exercise training improved resting cardiac dysfunction, but it did not attenuate the maladaptive RV changes, and rats subjected to HIIT accrued earlier and more deaths. Of note, these animals were without the benefit of therapy but support that more research at the cellular level is necessary and raises the suspicion of RV–PA uncoupling.[109]

RV–PA coupling is described as an incapacity of the RV to recruit contractile function in the face of elevated afterload. Research is needed because uncoupling may be associated with adverse RV remodeling and poor outcomes, and investigation of the effect of different workloads, physical postures, and etiology may ultimately lead to better exercise prescriptions.[110] To translate this data and use it more broadly, researchers need easier surrogates for cardiac MRI and CPET such as echo or lactate thresholds as done in elite athletes.

Lastly, exercise training needs to be more accessible at home. Several papers have been published in regard to inpatient rehab noting benefits but delivery and access need to be optimized. Home-based programs have advantages and disadvantages but have the potential to be just effective. In conclusion, exercise is beneficial in PH but needs to be studied to maintain RV–PA coupling during exercise and more research into remote monitoring tools to help optimize safety and efficacy.

THE ROLE OF CANNABINOIDS AND DIETARY SUPPLEMENTS IN PH CARE, ALISSA MARGRAF, PHARMD, BCACP

Dr. Margraf described the endocannabinoid system (ECS), which is a natural cannabis-like molecule produced by the body that is involved in physiological and

cognitive processes including in the vascular system. Plants have a similar plant-derived cannabinoid, phytocannabinoids, and mimic ECS in the body. CBD (cannabidiol) and THC (delta-9 tetrahydrocannabinol) are two more well-known of the greater than 60 phytocannabinoids and bind to cannabinoid receptors throughout the body causing varied physiological effects.

In the United States, CBD was approved in 2018 as an active ingredient in epidiolex, which was approved to treat two rare pediatric epileptic syndromes. Aside from this approved medication, there are many other theoretical uses. CBD has several therapeutic targets, animal models have demonstrated protective effects on the vascular endothelium, decrease in RVSP, and pulmonary artery hypertrophy, as well as vasorelaxant effects on the pulmonary arteries of deceased donors.[111–113] CBD has had promising results in animal models, but human randomized trials are still needed.

Consumer awareness of CBD is high but knowledge is poor. Most people use CBD to alleviate pain, improve mood or sleep, or for wellness, but concerningly >10% are using it to treat severe debilitating conditions, possibly putting off more appropriate care.[114] Around 2018 when epidiolex was approved by the FDA as a medication. CBD could no longer be labeled as a dietary supplement or added freely to food. However, the 2018 Farm Bill legalized hemp including its extracts and cannabinoids. This removed it from the list of federally controlled substances by the Drug Enforcement Agency allowing primarily state regulation. Hemp is considered any part of the cannabis plant with a THC concentration of <0.3% dry weight with limited psychoactivity and has many industrial and nonmedicinal uses.

There is widespread marketing, selling, and use of CBD. The FDA has warned several companies for illegally marketing and selling CBD products for clinical use and studies have also noted inaccuracies in content labels. A study noted only 31% of products sampled were within 10% of their labeled values and 18 out of 84 samples detected THC.[115] Many of our patients continue to use CBD and it may be prudent to give guidance to ensure product quality and safety. It is advised to look for third-party testing with good manufacturing practices including the source of CBD. Avoid products with health claims or labeling that it is derived from "plant" as that is illegal. It may also be advisable to consider monitoring transaminases with CBD use. Remember natural does not always mean safe or effective.

Lastly, there are many natural products in the market that can be very appealing. Many of these products may seem safer or have a cultural background. Some examples include St. John's wort, which can have several potentially serious cardiac drug interactions and is an inducer of the cytochrome pathways, which could affect the metabolism of many PAH medications, potentially decreasing their efficacy. Ma Huong or ephedra can cause vasoconstriction and increase blood pressure. Garlic, *Ginkgo biloba*, ginseng, and turmeric increase the risk of bleeding. Vitamin K may have untoward effects on the efficacy of warfarin. Kava, echinacea, and valerian root can cause liver damage.[116] A variety of fresh foods are a good source of vitamins and minerals and preferable to dietary supplements. Pharmacists are available to discuss supplements and potential medication interactions and are an integral piece of multidisciplinary care teams.

STATE-OF-THE-ART MECHANICAL CIRCULATORY SUPPORT FOR PH, DR. CHRISTIAN A. BERMUDEZ

PAH patients are among the most complicated patients to manage with mechanical circulatory support (MCS). Few options exist, and there is little time. It is well understood that chronic pressure overload leads to RV failure and mortality, and there is a relationship between hypoxemia in RV dysfunction and maladaptive response. The target to mechanically support patients historically has been focused on LV. In the 2000s, more innovation for RV support was in development and more recently mechanical support has been considered as a bridge to transplant.

Indications for MCS in PH include cardiogenic shock (CVP > 15 mmHg, increased inotropic requirements, decreased CI < 2.2), as well as progressive hypoxemia even before RV failure, especially as a bridge to transplant. MCS can also be considered as a bridge to recovery for patients with right to left shunts, acute pneumonia, ILD exacerbations, or other modifiable or reversible conditions. Most Group 3 and Group 5 patients typically bridge to transplant, but in some decompensated Group 1 and Group 4 patients, MCS may be an option for recovery particularly if they are medically under-treated, that is, need parenteral optimization or may be a thromboendarterectomy candidate. Regardless, the exit strategy from MCS needs to be clear from the beginning.

Device selection for temporary support depends on the presentation of the patient including the need for left, right, or biventricular support, urgency, vasculature accessibility for cannulation, flow needs, presence of hypoxemia, and availability of a device. Options include RV access device (RVAD), VA-ECMO, and VV-ECMO. Unfortunately, interventional lung assist Novalung, as

well as some other devices and technologies, are no longer available.[117]

The most frequently used device in PH is VA-ECMO for shock or profound hypoxemia. However, it is important to know that VA-ECMO contributes to retrograde flow, which can increase LVEDP and LVEDV and lead to pulmonary congestion and hypoxemia in patients with systolic or diastolic dysfunction.[118] Consideration for veno-arterial-venous hybrid VA ECMO may be an option in this patient population.[119] In the past 10 years, there has been a marked improvement in survival in the use of VA-ECMO in general.[120] However, a much higher risk of mortality remains in PAH patients, survival time on VA-ECMO is much shorter to about 10–14 days, although VV-ECMO may offer up to months as a bridge to transplant.[121–123]

Emerging as a viable option in PH, RVAD, or OxyRVADs, which adds an oxygenator for hypoxic patients, may improve survival citing successes along with VV ECMO in patients with RV dysfunction and COVID-19 ARDS-PH.[124,125] RVADs have not decreased RV size as much as hoped and there has been persistent tricuspid regurgitation making management tricky.[126] However, some good outcomes have been published for RVADs with various approaches as a bridge to transplant, but considerable challenges, including pump failure, cannula thrombosis, and tricuspid injuries, decrease suitability as a long-term therapy.[127,128] While there has been a loss of device access, there may be feasible use of LVAD technologies to successfully moderate lower flow long-term to pulmonary arteries.[129] In conclusion, there is increasing interest in MCS support with patients with PH, and available devices currently offer a viable option as a bridge to transplant or optimization of therapies with recovery but long-term support is far off and further studies are needed.

PEARLS AND PITFALLS IN LUNG TRANSPLANTATION FOR PH, DR. DEBORAH JO LEVINE

PH encompasses a diverse group of conditions that lead to elevated arterial and/or venous pulmonary pressures, although these diseases act differently, each etiology is considered separately. PH can be a leading indication for transplant as in PAH, or it may be associated with other conditions being considered for a transplant. The first lung transplant for PAH was performed in 1983.[130] Nationally there has been an exponential increase in transplants, and as time has gone on with the progression of newer drugs, PAH represents a smaller proportion of all lung transplants at about 2% compared to 15% before the mid-1990s.[131,132]

PAH remains a progressive disease and some patients will continue to require transplants despite therapy as they risk deterioration on maximal therapies. Before medication advancements, patients were introduced to transplants early and unfortunately are now more often referred to too late. The transplantation window is small in PAH, and patients may be too sick by the time they get to the transplant. Lung allocation score (LAS) is based on waitlist urgency, posttransplant survival, and diagnostic group. LAS does not accurately predict waitlist survival in PAH as hemodynamic parameters are not highly weighted but may qualify for some exception points. The LAS will soon be changed to be a continuous distribution, and it is unclear how this will affect the PAH population.

Ensuring that lung transplant is available to PAH patients includes introducing the idea early after diagnosis or with an escalation of therapy as these patients are unpredictable. It is important to remember that early referral does not mean premature transplantation. Dr. Levine recommends considering referral for lung transplant routinely with each risk evaluation. The ISHLT consensus suggested referral with increased risk score despite appropriate therapy, significant RV dysfunction, need for parenteral therapy, recent hospitalization for PAH, pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis, signs of heart failure or secondary organ dysfunction, and life-threatening complications such as hemoptysis.[133] In terms of success and improvement in survival, over the last several years mean survival among all-comers remains about the same.[131] However, when split out by disease state cystic fibrosis (CF) patients have the best survival, but conditional survival in PAH patients approaches that of CF, although PAH has higher perioperative mortality.[132] Earlier referral when patients are less ill when transplanted may improve perioperative and early postoperative complications.

In HFpEF and Group 2 PH there is a higher risk of high-grade primary graft dysfunction.[134] Connective tissue diseases such as scleroderma as well as sarcoidosis can also have direct cardiac involvement and left-sided disease and these patients may be difficult to treat post-transplant as well. Group 3 PH patients have the worst outcomes and patients with interstitial pneumonia and ILDs do worse than those with COPD or CPFE.[135] Patients with IPF and PH-ILD are particularly difficult and experience more progressive decline, referral timing is crucial because they may rapidly deteriorate.[135] Patients with PH-ILD also are often older and present with more comorbidities and should continue to be

comanaged with all specialists involved. Lastly, it is important to rule out CTEPH because endarterectomy is preferable to lung transplant in those patients and PTE may not disqualify them for transplant in the future.

AUTHORS CONTRIBUTIONS

All authors contributed equally to writing this paper. Evan Brittain is responsible for supervising the process of writing this manuscript.

CONFLICTS OF INTEREST

Evan Brittain has a conflict as he has a United Therapeutics investigator-initiated grant. Nicholas J. Shelburne received an investigator-initiated award from Bayer. Jennalyn D. Mayeux is on the Janssen PH and United Therapeutics speakers bureaus and has participated in advisory boards for GossamerBio, Liquidia, and Janssen PH. The remaining author declares no conflict of interest.

ETHICS STATEMENT

The ethics statement is not available.

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REFERENCES

1. Tapson VF, Sanchez Diaz CJ, Bohns Meyer GM, Pulido T, Sepulveda P, Wang KY, Deng CQ, Grover R, Solum D, Ousmanou A, White RJ. Treatment with oral treprostinil delays time to clinical worsening in patients with pulmonary arterial hypertension—results from FREEDOM-EV. J Heart Lung Transplant. 2019;38:S94–5.
2. Hoeper MM, Al-Hiti H, Benza RL, Chang SA, Corris PA, Gibbs JSR, Grünig E, Jansa P, Klinger JR, Langleben D, McLaughlin VV, Meyer GMB, Ota-Arakaki J, Peacock AJ, Pulido T, Rosenkranz S, Vizza CD, Vonk-Noordegraaf A, White RJ, Chang M, Kleinjung F, Meier C, Paraschin K, Ghofrani HA, Simonneau G, Olschewski H, Delcroix M, Andrade-Lima M, de Amorim Corrêac R, Figueiredo Campos F, Ota Arakaki J, Meyer G, De Souza R, Langleben D, Al-Hiti H, Jansa P, Mellemkjær S, Bauer F, Montani D, Simonneau G, Drömann D, Ghofrani HA, Grünig E, Halank M, Held M, Hoeper M, Klose H, Kneidinger N, Leuchte H, Opitz C, Rosenkranz S, Wilkens H, Wirtz H, Karvounis H, Pitsiou G, Orfanos S, D'Alto M, Ghio S, Vizza C, Vitulo P, Nakayama T, Maki H, Tatebe S, de los Rios Ibarra M, Pulido T, Van Dijk A, Vonk-Noordegraaf A, Roleder T, Castro G, Loureiro M, Robalo-Martins S, Barberá J, Lázaro M, Perez-Penate G, Román A, Cheng CC, Hsu CH, Hsu HH, Atahan E, Mogulkoc Bishop N, Okumus N, Onen Z, Chang HJ, Chang SA, Lee JS, Kim HK, Coghlan J, Corris P, Church A, Condliffe R, Gibbs J, Peacock A, Wort S, Allen R, Allen S, Awdish R, Benza R, DeSouza S, Feldman J, Johri S, Klinger J, Layish D, McConnell J, McLaughlin V, Migliore C, Rahaghi F, Rischard F, Robbins I, Satterwhite L, Shah T, Sulica R, White R. 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;9:573–84.
3. Chin KM, Sitbon O, Doelberg M, Feldman J, Gibbs JSR, Grünig E, Hoeper MM, Martin N, Mathai SC, McLaughlin VV, Perchenet L, Poch D, Saggar R, Simonneau G, Galiè N. Three-versus two-drug therapy for patients with newly diagnosed pulmonary arterial hypertension. J Am Coll Cardiol. 2021;78:1393–403.
4. Humbert M, McLaughlin V, Gibbs JSR, Gomberg-Maitland M, Hoeper MM, Preston IR, Souza R, Waxman A, Escribano Subias P, Feldman J, Meyer G, Montani D, Olsson KM, Manimaran S, Barnes J, Linde PG, de Oliveira Pena J, Badesch DB. Sotatercept for the treatment of pulmonary arterial hypertension. N Engl J Med. 2021;384:1204–15.
5. Anderson JJ, Lau EM, Lavender M, Benza R, Celermajer DS, Collins N, Corrigan C, Dwyer N, Feenstra J, Horrigan M, Keating D, Kermeen F, Kotlyar E, McWilliams T, Rhodes B, Steele P, Thakkar V, Williams T, Whitford H, Whyte K, Weintraub R, Wrobel JP, Keogh A, Strange G. Retrospective validation of the REVEAL 2.0 risk score with the Australian and New Zealand Pulmonary Hypertension Registry Cohort. Chest. 2020;157:162–72.
6. Benza RL, Kanwar MK, Raina A, Scott JV, Zhao CL, Selej M, Elliott CG, Farber HW. 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;159:337–46.
7. Maron BA, Abman SH, Elliott CG, Frantz RP, Hopper RK, Horn EM, Nicolls MR, Shlobin OA, Shah SJ, Kovacs G, Olschewski H, Rosenzweig EB. Pulmonary arterial hypertension: diagnosis, treatment, and novel advances. Am J Respir Crit Care Med. 2021;203:1472–87.
8. DuBrock HM, Burger CD, Bartolome SD, Feldman JP, Ivy DD, Rosenzweig EB, Sager JS, Presberg KW, Mathai SC, Lammi MR, Klinger JR, Eggert M, e Marco T, Elwing JM, Badesch D, Bull TM, Cadaret LM, Ramani G, Thenappan T, Ford HJ, Al-Naamani N, Simon MA, Mazimba S, Runo JR, Chakinala M, Horn EM, Ryan JJ, Frantz RP, Krowka MJ. Health disparities and treatment approaches in portopulmonary hypertension and idiopathic pulmonary arterial hypertension: an analysis of the Pulmonary Hypertension Association Registry. Pulm Circ. 2021;11:1–10.
9. Kolaitis NA, Lammi M, Mazimba S, Feldman J, McConnell W, Sager JS, Raval AA, Simon MA, De Marco T. HIV-associated pulmonary arterial hypertension: a report from the Pulmonary Hypertension Association Registry. Am J Respir Crit Care Med. 2022;205:1121–4.
10. Kolaitis NA, Zamanian RT, de Jesus Perez VA, Badesch DB, Benza RL, Burger CD, Chakinala MM, Elwing JM,

Feldman J, Lammi MR, Mathai SC, McConnell JW, Presberg KW, Robinson JC, Sager J, Shlobin OA, Simon MA, Kawut SM, Glidden DV, Singer JP, De Marco T. Clinical differences and outcomes between methamphetamine-associated and idiopathic pulmonary arterial hypertension in the pulmonary hypertension association registry. Ann Am Thorac Soc. 2021;18:613–22.

11. Min J, Badesch D, Chakinala M, Elwing J, Frantz R, Horn E, Klinger J, Lammi M, Mazimba S, Sager J, Shlobin O, Simon M, Thenappan T, Grinnan D, Ventetuolo C, Al-Naamani N, Raval A, Raina A, Hemnes A, Burger C, Dunbar Ivy D, Yung D, Zwicke D, Berman-Rosenzweig E, Ramani G, Farr G, James Ford H, Runo J, Fineman J, Feldman J, Swisher J, Ryan J, Wesley McConnell J, Presberg K, Parikh K, Cadaret L, Avdalovic M, Duncan M, Eggert M, Varghese N, Boyce P, Leary P, Foley R, James White R, Frantz R, Zamanian R, Hirsch R, Bakshi S, Bartolome S, Kawut S, Mathai S, De Marco T, Williamson T, Bull T. Prediction of health-related quality of life and hospitalization in pulmonary arterial hypertension: the Pulmonary Hypertension Association Registry. Am J Respir Crit Care Med. 2021;203:761–4.
12. Fakhri S, Hannon K, Moulden K, Peterson R, Hountras P, Bull T, Maloney J, De Marco T, Ivy D, Thenappan T, Sager JS, Ryan JJ, Mazimba S, Hirsch R, Chakinala M, Shlobin O, Lammi M, Zwicke D, Robinson J, Benza RL, Klinger J, Grinnan D, Mathai S, Badesch D. Residence at moderately high altitude and its relationship with WHO Group 1 pulmonary arterial hypertension symptom severity and clinical characteristics: the Pulmonary Hypertension Association Registry. Pulm Circ. 2020;10:1–8.
13. Olsson KM, Hoeper MM, Pausch C, Grünig E, Huscher D, Pittrow D, Rosenkranz S, Gall H. Pulmonary vascular resistance predicts mortality in patients with pulmonary hypertension associated with interstitial lung disease: results from the COMPERA registry. Eur Respir J. 2021;58:2101483.
14. Hoeper MM, Pausch C, Grünig E, Staehler G, Huscher D, Pittrow D, Olsson KM, Vizza CD, Gall H, Distler O, Opitz C, Gibbs JSR, Delcroix M, Ghofrani HA, Rosenkranz S, Park DH, Ewert R, Kaemmerer H, Lange TJ, Kabitz HJ, Skowasch D, Skride A, Claussen M, Behr J, Milger K, Halank M, Wilkens H, Seyfarth HJ, Held M, Dumitrescu D, Tsangaris I, Vonk-Noordegraaf A, Ulrich S, Klose H. Temporal trends in pulmonary arterial hypertension: results from the COMPERA registry. Eur Respir J. 2022;59:2102024.
15. Boucly A, Savale L, Jaïs X, Bauer F, Bergot E, Bertoletti L, Beurnier A, Bourdin A, Bouvaist H, Bulifon S, Chabanne C, Chaouat A, Cottin V, Dauphin C, Degano B, De Groote P, Favrolt N, Feng Y, Horeau-Langlard D, Jevnikar M, Jutant EM, Liang Z, Magro P, Mauran P, Moceri P, Mornex JF, Palat S, Parent F, Picard F, Pichon J, Poubeau P, Prévot G, Renard S, Reynaud-Gaubert M, Riou M, Roblot P, Sanchez O, Seferian A, Tromeur C, Weatherald J, Simonneau G, Montani D, Humbert M, Sitbon O. Association between initial treatment strategy and long-term survival in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2021;204:842–54.
16. Chen H, Shiboski SC, Golden JA, Gould MK, Hays SR, Hoopes CW, De Marco T. Impact of the lung allocation score on lung transplantation for pulmonary arterial hypertension. Am J Respir Crit Care Med. 2009;180:468–74.
17. Kolaitis NA, Chen H, Calabrese DR, Kumar K, Obata J, Bach C, Golden JA, Simon MA, Kukreja J, Hays SR, Leard LE, Singer JP, De Marco T. The lung allocation score remains inequitable for patients with PAH, even after the 2015 revision. Am J Respir Crit Care Med. 2022. https://doi.org/10.1164/rccm.202201-0217OC
18. Van der Feen DE, Kurakula K, Tremblay E, Boucherat O, Bossers GPL, Szulcek R, Bourgeois A, Lampron MC, Habbout K, Martineau S, Paulin R, Kulikowski E, Jahagirdar R, Schalij I, Bogaard HJ, Bartelds B, Provencher S, Berger RMF, Bonnet S, Goumans MJ. Multicenter preclinical validation of BET inhibition for the treatment of pulmonary arterial hypertension. Am J Respir Crit Care Med. 2019;200:910–20.
19. Provencher S, Potus F, Blais-Lecours P, Bernard S, Martineau S, Breuils-Bonnet S, Weatherald J, Sweeney M, Kulikowski E, Boucherat O, Bonnet S. BET protein inhibition for pulmonary arterial hypertension: a pilot study. Am J Respir Crit Care Med. 2022;205(11):1357–60.
20. Di Micco R, Krizhanovsky V, Baker D, d'Adda di Fagagna F. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. Nat Rev Mol Cell Biol. 2021;22:75–95.
21. Van Der Feen DE, Bossers GPL, Hagdorn QAJ, Moonen JR, Kurakula K, Szulcek R, Chappell J, Vallania F, Donato M, Kok K, Kohli JS, Petersen AH, van Leusden T, Demaria M, Goumans MJTH, De Boer RA, Khatri P, Rabinovitch M, Berger RMF, Bartelds B. Cellular senescence impairs the reversibility of pulmonary arterial hypertension. Sci Transl Med. 2020;12:eaaw4974.
22. Kim S, Rigatto K, Gazzana MB, Knorst MM, Richards EM, Pepine CJ, Raizada MK. Altered gut microbiome profile in patients with pulmonary arterial hypertension. Hypertension. 2020;75:1063–71.
23. Huang Y, Lin F, Tang R, Bao C, Zhou Q, Ye K, Shen Y, Liu C, Hong C, Yang K, Tang H, Wang J, Lu W, Wang T. Gut microbial metabolite trimethylamine N-oxide aggravates pulmonary hypertension. Am J Respir Cell Mol Biol. 2022;66:452–60.
24. Anderson JH, Cabalka AK, Frantz RP, Cajigas HR, Taggart NW. Transcatheter nonductal reverse Potts shunt creation in pulmonary arterial hypertension. Circ Cardiovasc Interv. 2022;15:e011315.
25. Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, Peacock AJ, Simonneau G, Vachiery JL, Grünig E, Oudiz RJ, Vonk-Noordegraaf A, White RJ, Blair C, Gillies H, Miller KL, Harris JHN, Langley J, Rubin LJ. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med. 2015;373:834–44.
26. Hoeper MM, Ghofrani H-A, Al-Hiti H, Benza R. Late breaking abstract-switching from PDE5i to riociguat in patients with PAH: the REPLACE study. Eur Respiratory Soc. 2020;56(suppl 64):3802.
27. Hoeper MM, Simonneau G, Corris PA, Ghofrani HA, Klinger JR, Langleben D, Naeije R, Jansa P, Rosenkranz S, Scelsi L, Grünig E, Vizza CD, Chang M, Colorado P, Meier C, Busse D, Benza RL. RESPITE: switching to riociguat in pulmonary arterial hypertension patients with inadequate

response to phosphodiesterase-5 inhibitors. Eur Respir J. 2017;50:1602425.
28. Vonk Noordegraaf A, Channick R, Cottreel E, Kiely DG, Marcus JT, Martin N, Moiseeva O, Peacock A, Swift AJ, Tawakol A, Torbicki A, Rosenkranz S, Galiè N. The REPAIR study: effects of macitentan on RV structure and function in pulmonary arterial hypertension. JACC Cardiovasc Imaging. 2022;15:240–53.
29. Sehgal S, Chowdhury A, Rabih F, Gadre A, Park MM, Li M, Wang X, Highland KB. Counting steps: a new way to monitor patients with pulmonary arterial hypertension. Lung. 2019;197:501–8.
30. Howard LS, Rosenkranz S, Frantz RP, Hemnes AR, Pfister T, Schmitz S-FH, Skåra H, Humbert M, Preston IR. Assessing daily life physical activity by actigraphy in pulmonary arterial hypertension: insights from the randomized controlled study with selexipag (TRACE). Chest. 2022;S0012-3692(22):03707-2. https://doi.org/10.1016/j.chest.2022.08.2231
31. Troosters T, Bourbeau J, Maltais F, Leidy N, Erzen D, De Sousa D, Korducki L, Hamilton A. Enhancing exercise tolerance and physical activity in COPD with combined pharmacological and non-pharmacological interventions: PHYSACTO randomised, placebo-controlled study design. BMJ Open. 2016;6:e010106.
32. Gichoya JW, Banerjee I, Bhimireddy AR, Burns JL, Celi LA, Chen LC, Correa R, Dullerud N, Ghassemi M, Huang SC, Kuo PC, Lungren MP, Palmer LJ, Price BJ, Purkayastha S, Pyrros AT, Oakden-Rayner L, Okechukwu C, Seyyed-Kalantari L, Trivedi H, Wang R, Zaiman Z, Zhang H. AI recognition of patient race in medical imaging: a modelling study. Lancet Digital Health. 2022;4:e406–14.
33. Kiely DG, Doyle O, Drage E, Jenner H, Salvatelli V, Daniels FA, Rigg J, Schmitt C, Samyshkin Y, Lawrie A, Bergemann R. Utilising artificial intelligence to determine patients at risk of a rare disease: idiopathic pulmonary arterial hypertension. Pulm Circ. 2019;9:1–9.
34. Leopold JA, Loscalzo J. Emerging role of precision medicine in cardiovascular disease. Circ Res. 2018;122:1302–15.
35. Cheng F, Desai RJ, Handy DE, Wang R, Schneeweiss S, Barabási A, Loscalzo J. Network-based approach to prediction and population-based validation of in silico drug repurposing. Nat Commun. 2018;9:2691.
36. Sitbon O, Jais X, Savale L, Cottin V, Bergot E, Macari EA, Bouvaist H, Dauphin C, Picard F, Bulifon S, Montani D, Humbert M, Simonneau G. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. Eur Respir J. 2014;43:1691–97. https://doi.org/10.1183/09031936.00116313
37. Olsson KM, Richter MJ, Kamp JC, Gall H, Heine A, Ghofrani HA, Fuge J, Ewert R, Hoeper MM. Intravenous treprostinil as an add-on therapy in patients with pulmonary arterial hypertension. J Heart Lung Transplant. 2019;38:748–56. https://doi.org/10.1016/j.healun.2019.05.002
38. D'Alto M, Badagliacca R, Argiento P, Romeo E, Farro A, Papa S, Sarubbi B, Russo MG, Vizza CD, Golino P, Naeije R. Risk reduction and right heart reverse remodeling by upfront triple combination therapy in pulmonary arterial hypertension. Chest. 2020;157:376–83. https://doi.org/10.1016/j.chest.2019.09.009
39. van de Veerdonk MC, Kind T, Marcus JT, Mauritz GJ, Heymans MW, Bogaard HJ, Boonstra A, Marques KMJ, Westerhof N, Vonk-Noordegraaf A. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. J Am Coll Cardiol. 2011;58:2511–9. https://doi.org/10.1016/j.jacc.2011.06.068
40. van de Veerdonk MC, Marcus JT, Westerhof N, de Man FS, Boonstra A, Heymans MW, Bogaard HJ, Vonk Noordegraaf A. Signs of right ventricular deterioration in clinically stable patients with pulmonary arterial hypertension. Chest. 2015;147:1063–71. https://doi.org/10.1378/chest.14-0701
41. Badagliacca R, Poscia R, Pezzuto B, Papa S, Reali M, Pesce F, Manzi G, Gianfrilli D, Ciciarello F, Sciomer S, Biondi-Zoccai G, Torre R, Fedele F, Vizza CD. Prognostic relevance of right heart reverse remodeling in idiopathic pulmonary arterial hypertension. J Heart Lung Transplant. 2018;37:195–205. https://doi.org/10.1016/j.healun.2017.09.026
42. McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. N Engl J Med. 1998;338:273–7. https://doi.org/10.1056/nejm199801293380501
43. Tapson VF, Gomberg-Maitland M, McLaughlin VV, Benza RL, Widlitz AC, Krichman A, Barst RJ. Safety and efficacy of IV treprostinil for pulmonary arterial hypertension. Chest. 2006;129:683–8. https://doi.org/10.1378/chest.129.3.683
44. Badagliacca R, D'Alto M, Ghio S, Argiento P, Bellomo V, Brunetti ND, Casu G, Confalonieri M, Corda M, Correale M, D'Agostino C, De Michele L, Galgano G, Greco A, Lombardi C, Manzi G, Mercurio V, Mulè M, Paciocco G, Papa S, Romeo E, Scelsi L, Stolfo D, Vitulo P, Naeije R, Vizza CD. Risk reduction and hemodynamics with initial combination therapy in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2021;203:484–92. https://doi.org/10.1164/rccm.202004-1006OC
45. Tuckson RV, Edmunds M, Hodgkins ML. Telehealth. N Engl J Med. 2017;377:1585–92. https://doi.org/10.1056/NEJMsr1503323
46. Sahay S, Shlobin OA, Levine DJ, Poms A, Soto FJ, Melendres-Groves L, Mullin CJ, Bossone E, Balasubramanian V, Memon HA, Kay D, Mathai SC, Highland KB, Elwing JM. Impact of COVID-19 pandemic on care of pulmonary hypertension patients. In: D106 Noe valley: clots, covid, and lung vascular diseases, Abstract presented at the American Thoracic Society International Conference. ATS Journal; 2022. p. A5421.
47. Battineni G, Sagaro GG, Chintalapudi N, Amenta F. The benefits of telemedicine in personalized prevention of cardiovascular diseases (CVD): a systematic review. J Pers Med. 2021;11:658. https://doi.org/10.3390/jpm11070658
48. Wesley Milks M, Sahay S, Benza RL, Farber HW. Risk assessment in patients with pulmonary arterial hypertension in the era of COVID 19 pandemic and the telehealth revolution: state of the art review. J Heart Lung Transplant. 2021;40:172–82. https://doi.org/10.1016/j.healun.2020.12.005
49. Zhang T, Mosier J, Subbian V. Identifying barriers to and opportunities for telehealth implementation amidst the

COVID-19 pandemic by using a human factors approach: a leap into the future of health care delivery? JMIR Hum Factors. 2021;8:e24860.

50. Grady RM, Canter MW, Wan F, Shmalts AA, Coleman RD, Beghetti M, Berger RMF, del Cerro Marin MJ, Fletcher SE, Hirsch R, Humpl T, Ivy DD, Kirkpatrick EC, Kulik TJ, Levy M, Moledina S, Yung D, Eghtesady P, Bonnet D, Magness SM, Anderson VR, Mullen MM, Gorbachevsky SV, Zaets SB, Haarman MG, Szezepanski I. Pulmonary-to-Systemic arterial shunt to treat children with severe pulmonary hypertension. J Am Coll Cardiol. 2021;78:468–77. https://doi.org/10.1016/j.jacc.2021.05.039
51. Majeed RW, Wilkins MR, Howard L, Hassoun PM, Anthi A, Cajigas HR, Cannon J, Chan SY, Damonte V, Elwing J, Förster K, Frantz R, Ghio S, Al Ghouleh I, Hilgendorff A, Jose A, Juaneda E, Kiely DG, Lawrie A, Orfanos SE, Pepe A, Pepke-Zaba J, Sirenko Y, Swett AJ, Torbas O, Zamanian RT, Marquardt K, Michel-Backofen A, Antoine T, Wilhelm J, Barwick S, Krieb P, Fuenderich M, Fischer P, Gall H, Ghofrani HA, Grimminger F, Tello K, Richter MJ, Seeger W. Pulmonary vascular research institute GoDeep: a meta-registry merging deep phenotyping data from international PH reference centers. Pulm Circ. 2022;12:e12123. https://doi.org/10.1002/pul2.12123
52. Nadrous HF, Pellikka PA, Krowka MJ, Swanson KL, Chaowalit N, Decker PA, Ryu JH. The impact of pulmonary hypertension on survival in patients with idiopathic pulmonary fibrosis. Chest. 2005;128:616S–7S. https://doi.org/10.1378/chest.128.6_suppl.616S-a
53. Patel NM, Lederer DJ, Borczuk AC, Kawut SM. Pulmonary hypertension in idiopathic pulmonary fibrosis. Chest. 2007;132:998–1006. https://doi.org/10.1378/chest.06-3087
54. Nathan SD, Shlobin OA, Ahmad S, Urbanek S, Barnett SD. Pulmonary hypertension and pulmonary function testing in idiopathic pulmonary fibrosis. Chest. 2007;131:657–63. https://doi.org/10.1378/chest.06-2485
55. Raghu G, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, Martinez FJ, Nathan SD, Wells AU, Collard HR, Costabel U, Richeldi L, de Andrade J, Khalil N, Morrison LD, Lederer DJ, Shao L, Li X, Pedersen PS, Montgomery AB, Chien JW, O'Riordan TG. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann Intern Med. 2013;158:641–9. https://doi.org/10.7326/0003-4819-158-9-201305070-00003
56. Ghofrani HA, Wiedemann R, Rose F, Schermuly RT, Olschewski H, Weissmann N, Gunther A, Walmrath D, Seeger W, Grimminger F. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. Lancet. 2002;360:895–900. https://doi.org/10.1016/s0140-6736(02)11024-5
57. Kolb M, Raghu G, Wells AU, Behr J, Richeldi L, Schinzel B, Quaresma M, Stowasser S, Martinez FJ. Nintedanib plus sildenafil in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2018;379:1722–31. https://doi.org/10.1056/NEJMoa1811737
58. Waxman A, Restrepo-Jaramillo R, Thenappan T, Ravichandran A, Engel P, Bajwa A, Allen R, Feldman J, Argula R, Smith P, Rollins K, Deng C, Peterson L, Bell H, Tapson V, Nathan SD. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. N Engl J Med. 2021;384:325–34. https://doi.org/10.1056/NEJMoa2008470
59. Arcasoy SM, Christie JD, Ferrari VA, Sutton MSJ, Zisman DA, Blumenthal NP, Pochettino A, Kotloff RM. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med. 2003;167:735–40. https://doi.org/10.1164/rccm.200210-1130OC
60. Bhatia KD, Ambati C, Dhaliwal R, Paschkewitz R, Hsu E, Ho B, Young A, Emmett L. SPECT-CT/VQ versus CTPA for diagnosing pulmonary embolus and other lung pathology: pre-existing lung disease should not be a contraindication. J Med Imaging Radiat Oncol. 2016;60:492–7. https://doi.org/10.1111/1754-9485.12471
61. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53:1801913. https://doi.org/10.1183/13993003.01913-2018
62. Maron BA, Hess E, Maddox TM, Opotowsky AR, Tedford RJ, Lahm T, Joynt KE, Kass DJ, Stephens T, Stanislawski MA, Swenson ER, Goldstein RH, Leopold JA, Zamanian RT, Elwing JM, Plomondon ME, Grunwald GK, Barón AE, Rumsfeld JS, Choudhary G. Association of borderline pulmonary hypertension with mortality and hospitalization in a large patient cohort: insights from the veterans affairs clinical assessment, reporting, and tracking program. Circulation. 2016;133:1240–8. https://doi.org/10.1161/circulationaha.115.020207
63. Assad TR, Maron BA, Robbins IM, Xu M, Huang S, Harrell FE, Farber-Eger EH, Wells QS, Choudhary G, Hemnes AR, Brittain EL. Prognostic effect and longitudinal hemodynamic assessment of borderline pulmonary hypertension. JAMA Cardiol. 2017;2:1361–8. https://doi.org/10.1001/jamacardio.2017.3882
64. Douschan P, Kovacs G, Avian A, Foris V, Gruber F, Olschewski A, Olschewski H. Mild elevation of pulmonary arterial pressure as a predictor of mortality. Am J Respir Crit Care Med. 2018;197:509–16. https://doi.org/10.1164/rccm.201706-1215OC
65. Valerio CJ, Schreiber BE, Handler CE, Denton CP, Coghlan JG. Borderline mean pulmonary artery pressure in patients with systemic sclerosis: transpulmonary gradient predicts risk of developing pulmonary hypertension. Arthritis Rheum. 2013;65:1074–84. https://doi.org/10.1002/art.37838
66. Jaafar S, Visovatti S, Young A, Huang S, Cronin P, Vummidi D, McLaughlin V, Khanna D. Impact of the revised haemodynamic definition on the diagnosis of pulmonary hypertension in patients with systemic sclerosis. Eur Respir J. 2019;54:1900586. https://doi.org/10.1183/13993003.00586-2019
67. Montané BE, Fiore AM, Reznicek EC, Jain V, Jellis C, Rokadia H, Li M, Wang X, Dweik R, Loh E, Watkins AC, Haddad F, Amsallem M, Zamanian RT, Perez VJ, Heresi GA. Optimal tricuspid regurgitation velocity to screen for pulmonary hypertension in tertiary referral centers. Chest. 2021;160:2209–19. https://doi.org/10.1016/j.chest.2021.06.046

68. Coghlan JG, Denton CP, Grünig E, Bonderman D, Distler O, Khanna D, Müller-Ladner U, Pope JE, Vonk MC, Doelberg M, Chadha-Boreham H, Heinzl H, Rosenberg DM, McLaughlin VV, Seibold JR. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis. 2014;73:1340–49. https://doi.org/10.1136/annrheumdis-2013-203301
69. Young A, Moles VM, Jaafar S, Visovatti S, Huang S, Vummidi D, Nagaraja V, McLaughlin V, Khanna D. Performance of the DETECT Algorithm for pulmonary hypertension screening in a systemic sclerosis cohort. Arthritis Rheumatol. 2021;73:1731–7. https://doi.org/10.1002/art.41732
70. Pan Z, Marra AM, Benjamin N, Eichstaedt CA, Blank N, Bossone E, Cittadini A, Coghlan G, Denton CP, Distler O, Egenlauf B, Fischer C, Harutyunova S, Xanthouli P, Lorenz HM, Grünig E. Early treatment with ambrisentan of mildly elevated mean pulmonary arterial pressure associated with systemic sclerosis: a randomized, controlled, double-blind, parallel group study (EDITA study). Arthritis Res Ther. 2019;21:217. https://doi.org/10.1186/s13075-019-1981-0
71. Hassoun PM, Zamanian RT, Damico R, Lechtzin N, Khair R, Kolb TM, Tedford RJ, Hulme OL, Housten T, Pisanello C, Sato T, Pullins EH, Corona-Villalobos CP, Zimmerman SL, Gashouta MA, Minai OA, Torres F, Girgis RE, Chin K, Mathai SC. Ambrisentan and tadalafil up-front combination therapy in scleroderma-associated pulmonary arterial hypertension. Am J Respir Crit Care Med. 2015;192:1102–10. https://doi.org/10.1164/rccm.201507-1398OC
72. Strange G, Playford D, Stewart S, Deague JA, Nelson H, Kent A, Gabbay E. Pulmonary hypertension: prevalence and mortality in the Armadale echocardiography cohort. Heart. 2012;98:1805–11. https://doi.org/10.1136/heartjnl-2012-301992
73. Wijeratne DT, Lajkosz K, Brogly SB, Lougheed MD, Jiang L, Housin A, Barber D, Johnson A, Doliszny KM, Archer SL. Increasing incidence and prevalence of World Health Organization Groups 1 to 4 pulmonary hypertension: a Population-Based Cohort Study in Ontario, Canada. Circ Cardiovasc Qual Outcomes. 2018;11:e003973. https://doi.org/10.1161/circoutcomes.117.003973
74. Huston JH, Shah SJ. Understanding the pathobiology of pulmonary hypertension due to left heart disease. Circ Res. 2022;130:1382–403. https://doi.org/10.1161/circresaha.122.319967
75. Thenappan T, Prins KW, Cogswell R, Shah SJ. Pulmonary hypertension secondary to heart failure with preserved ejection fraction. Can J Cardiol. 2015;31:430–9. https://doi.org/10.1016/j.cjca.2014.12.028
76. Gerges C, Gerges M, Lang MB, Zhang Y, Jakowitsch J, Probst P, Maurer G, Lang IM. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. Chest. 2013;143:758–66. https://doi.org/10.1378/chest.12-1653
77. Fayyaz AU, Edwards WD, Maleszewski JJ, Konik EA, DuBrock HM, Borlaug BA, Frantz RP, Jenkins SM, Redfield MM. Global pulmonary vascular remodeling in pulmonary hypertension associated with heart failure and preserved or reduced ejection fraction. Circulation. 2018;137:1796–810. https://doi.org/10.1161/circulationaha.117.031608
78. Assad TR, Hemnes AR, Larkin EK, Glazer AM, Xu M, Wells QS, Farber-Eger EH, Sheng Q, Shyr Y, Harrell FE, Newman JH, Brittain EL. Clinical and biological insights into combined post- and pre-capillary pulmonary hypertension. J Am Coll Cardiol. 2016;68:2525–36. https://doi.org/10.1016/j.jacc.2016.09.942
79. Gerges M, Gerges C, Pistritto AM, Lang MB, Trip P, Jakowitsch J, Binder T, Lang IM. Pulmonary hypertension in heart failure. Epidemiology, right ventricular function, and survival. Am J Respir Crit Care Med. 2015;192:1234–46. https://doi.org/10.1164/rccm.201503-0529OC
80. Gorter TM, Obokata M, Reddy YNV, Melenovsky V, Borlaug BA. Exercise unmasks distinct pathophysiologic features in heart failure with preserved ejection fraction and pulmonary vascular disease. Eur Heart J. 2018;39:2825–35. https://doi.org/10.1093/eurheartj/ehy331
81. Vanderpool RR, Saul M, Nouraie M, Gladwin MT, Simon MA. Association between hemodynamic markers of pulmonary hypertension and outcomes in heart failure with preserved ejection fraction. JAMA Cardiol. 2018;3:298–306. https://doi.org/10.1001/jamacardio.2018.0128
82. Cao JY, Wales KM, Cordina R, Lau EMT, Celermajer DS. Pulmonary vasodilator therapies are of no benefit in pulmonary hypertension due to left heart disease: a meta-analysis. Int J Cardiol. 2018;273:213–20. https://doi.org/10.1016/j.ijcard.2018.09.043
83. Guay CA, Morin-Thibault LV, Bonnet S, Lacasse Y, Lambert C, Lega JC, Provencher S. Pulmonary hypertension-targeted therapies in heart failure: a systematic review and meta-analysis. PLoS One. 2018;13:e0204610. https://doi.org/10.1371/journal.pone.0204610
84. Braunwald E. Gliflozins in the management of cardiovascular disease. N Engl J Med. 2022;386:2024–34. https://doi.org/10.1056/NEJMra2115011
85. Satoh T, Wang L, Espinosa-Diez C, Wang B, Hahn SA, Noda K, Rochon ER, Dent MR, Levine AR, Baust JJ, Wyman S, Wu YL, Triantafyllou GA, Tang Y, Reynolds M, Shiva S, Hilaire CS, Gomez D, Goncharov DA, Goncharova EA, Chan SY, Straub AC, Lai YC, McTiernan CF, Gladwin MT. Metabolic syndrome mediates ROS-miR-193b-NFYA-dependent downregulation of soluble guanylate cyclase and contributes to exercise-induced pulmonary hypertension in heart failure with preserved ejection fraction. Circulation. 2021;144:615–37. https://doi.org/10.1161/circulationaha.121.053889
86. Burkhoff D, Borlaug BA, Shah SJ, Zolty R, Tedford RJ, Thenappan T, Zamanian RT, Mazurek JA, Rich JD, Simon MA, Chung ES, Raza F, Majure DT, Lewis GD, Preston IR, Rich S. Levosimendan improves hemodynamics and exercise tolerance in PH-HFpEF. JACC Heart Fail. 2021;9:360–70. https://doi.org/10.1016/j.jchf.2021.01.015
87. McLaughlin VV, Langer A, Tan M, Clements PJ, Oudiz RJ, Tapson VF, Channick RN, Rubin LJ. Contemporary trends in the diagnosis and management of pulmonary arterial hypertension. Chest. 2013;143:324–32. https://doi.org/10.1378/chest.11-3060

88. Tunariu N, Gibbs SJR, Win Z, Gin-Sing W, Graham A, Gishen P, AL-Nahhas A. Ventilation–perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med. 2007;48: 680–4. https://doi.org/10.2967/jnumed.106.039438
89. Kim NH, Delcroix M, Jenkins DP, Channick R, Dartevelle P, Jansa P, Lang I, Madani MM, Ogino H, Pengo V, Mayer E. Chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol. 2013;62:D92–9. https://doi.org/10.1016/j.jacc.2013.10.024
90. Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, Ogo T, Tapson VF, Ghofrani HA, Jenkins DP. Chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019;53:1801915. https://doi.org/10.1183/13993003.01915-2018
91. Olschewski H, Simonneau G, Galiè N, Higenbottam T, Naeije R, Rubin LJ, Nikkho S, Speich R, Hoeper MM, Behr J, Winkler J, Sitbon O, Popov W, Ghofrani HA, Manes A, Kiely DG, Ewert R, Meyer A, Corris PA, Delcroix M, Gomez-Sanchez M, Siedentop H, Seeger W. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med. 2002;347: 322–9. https://doi.org/10.1056/NEJMoa020204
92. Jaïs X, D'Armini AM, Jansa P, Torbicki A, Delcroix M, Ghofrani HA, Hoeper MM, Lang IM, Mayer E, Pepke-Zaba J, Perchenet L, Morganti A, Simonneau G, Rubin LJ. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol. 2008;52:2127–34. https://doi.org/10.1016/j.jacc.2008.08.059
93. Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, Mayer E, Simonneau G, Wilkins MR, Fritsch A, Neuser D, Weimann G, Wang C. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med. 2013;369:319–29. https://doi.org/10.1056/NEJMoa1209657
94. Ghofrani HA, Simonneau G, D'Armini AM, Fedullo P, Howard LS, Jaïs X, Jenkins DP, Jing ZC, Madani MM, Martin N, Mayer E, Papadakis K, Richard D, Kim NH, Lang I, Kähler C, Delcroix M, Bshouty Z, Varela PS, Jing ZC, Yang Y, Liu J, Zhang G, Zhang N, Mi Y, Zhu X, Jansa P, Jaïs X, Prévot G, Bouvaist H, Sanchez O, Grimminger F, Held M, Wilkens H, Rosenkranz S, Grünig E, Karlócai K, Temesvári A, Edes I, Aidietienė S, Miliauskas S, Zamudio TRP, Sanchez CJ, Noordegraaf AV, Lewczuk J, Podolec P, Kasprzak J, Mularek-Kubzdela T, Grzywna R, Dheda K, Moiseeva O, Chernyavskiy A, Shipulin V, Barbarash O, Martynyuk T, Kim HK, Park JB, Lee JS, Speich R, Ulrich S, Aubert JD, Phrommintikul A, Jaimchariyatam N, Sompradeekul S, Onen ZP, Okumus G, Solovey L, Gavrysyuk V, Howard L, Pepke-Zaba J, Condliffe R, McConnell J, Kerr K, Nguyen LH, Pham NV. Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. Lancet Respir Med. 2017;5:785–94. https://doi.org/10.1016/s2213-2600(17)30305-3
95. Sadushi-Kolici R, Jansa P, Kopec G, Torbicki A, Skoro-Sajer N, Campean IA, Halank M, Simkova I, Karlocai K, Steringer-Mascherbauer R, Samarzija M, Salobir B, Klepetko W, Lindner J, Lang IM. Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH): a double-blind, phase 3, randomised controlled trial. Lancet Respir Med. 2019;7: 239–48. https://doi.org/10.1016/s2213-2600(18)30367-9
96. Ogo T, Shimokawahara H, Kinoshita H, Sakao S, Abe K, Matoba S, Motoki H, Takama N, Ako J, Ikeda Y, Joho S, Maki H, Saeki T, Sugano T, Tsujino I, Yoshioka K, Shiota N, Tanaka S, Yamamoto C, Tanabe N, Tatsumi K. Selexipag for the treatment of chronic thromboembolic pulmonary hypertension. Eur Respir J. 2022;60:2101694. https://doi.org/10.1183/13993003.01694-2021
97. Jaïs X, Brenot P, Bouvaist H, Jevnikar M, Canuet M, Chabanne C, Chaouat A, Cottin V, De Groote P, Favrolt N, Horeau-Langlard D, Magro P, Savale L, Prévot G, Renard S, Sitbon O, Parent F, Trésorier R, Tromeur C, Piedvache C, Grimaldi L, Fadel E, Montani D, Humbert M, Simonneau G. Balloon pulmonary angioplasty versus riociguat for the treatment of inoperable chronic thromboembolic pulmonary hypertension (RACE): a multicentre, phase 3, open-label, randomised controlled trial and ancillary follow-up study. Lancet Respir Med. 2022;10:961–71. https://doi.org/10.1016/s2213-2600(22)00214-4
98. Feinstein JA, Goldhaber SZ, Lock JE, Ferndandes SM, Landzberg MJ. Balloon pulmonary angioplasty for treatment of chronic thromboembolic pulmonary hypertension. Circulation. 2001;103:10–3. https://doi.org/10.1161/01.cir.103.1.10
99. Aoki T, Sugimura K, Tatebe S, Miura M, Yamamoto S, Yaoita N, Suzuki H, Sato H, Kozu K, Konno R, Miyata S, Nochioka K, Satoh K, Shimokawa H. Comprehensive evaluation of the effectiveness and safety of balloon pulmonary angioplasty for inoperable chronic thromboembolic pulmonary hypertension: long-term effects and procedure-related complications. Eur Heart J. 2017;38: 3152–9. https://doi.org/10.1093/eurheartj/ehx530
100. Khan MS, Amin E, Memon MM, Yamani N, Siddiqi TJ, Khan SU, Murad MH, Mookadam F, Figueredo VM, Doukky R, Benza RL, Krasuski RA. Meta-analysis of use of balloon pulmonary angioplasty in patients with inoperable chronic thromboembolic pulmonary hypertension. Int J Cardiol. 2019;291:134–9. https://doi.org/10.1016/j.ijcard.2019.02.051
101. Kawakami T, Ogawa A, Miyaji K, Mizoguchi H, Shimokawahara H, Naito T, Oka T, Yunoki K, Munemasa M, Matsubara H. Novel angiographic classification of each vascular lesion in chronic thromboembolic pulmonary hypertension based on selective angiogram and results of balloon pulmonary angioplasty. Circ Cardiovasc Interv. 2016;9:e003318. https://doi.org/10.1161/circinterventions.115.003318
102. Mahmud E, Patel M, Ang L, Poch D. Advances in balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension. Pulm Circ. 2021;11:1–9. https://doi.org/10.1177/20458940211007385
103. Ito R, Yamashita J, Sasaki Y, Ikeda S, Suzuki S, Murata N, Ogino H, Chikamori T. Efficacy and safety of balloon pulmonary angioplasty for residual pulmonary hypertension after pulmonary endarterectomy. Int J Cardiol. 2021;334: 105–9. https://doi.org/10.1016/j.ijcard.2021.04.013

104. Nogueira-Ferreira R, Ferreira R, Padrão AI, Oliveira P, Santos M, Kavazis AN, Vitorino R, Moreira-Gonçalves D. One year of exercise training promotes distinct adaptations in right and left ventricle of female Sprague–Dawley rats. J Physiol Biochem. 2019;75:561–72. https://doi.org/10.1007/s13105-019-00705-4
105. Benito B, Gay-Jordi G, Serrano-Mollar A, Guasch E, Shi Y, Tardif JC, Brugada J, Nattel S, Mont L. Cardiac arrhythmogenic remodeling in a rat model of long-term intensive exercise training. Circulation. 2011;123:13–22. https://doi.org/10.1161/circulationaha.110.938282
106. Sanz-de la Garza M, Rubies C, Batlle M, Bijnens BH, Mont L, Sitges M, Guasch E. Severity of structural and functional right ventricular remodeling depends on training load in an experimental model of endurance exercise. Am J Physiol Heart Circ Physiol. 2017;313:H459–68. https://doi.org/10.1152/ajpheart.00763.2016
107. Nishizaki M, Ogawa A, Matsubara H. High right ventricular afterload during exercise in patients with pulmonary arterial hypertension. J Clin Med. 2021;10:2024. https://doi.org/10.3390/jcm10092024
108. Brown MB, Neves E, Long G, Graber J, Gladish B, Wiseman A, Owens M, Fisher AJ, Presson RG, Petrache I, Kline J, Lahm T. High-intensity interval training, but not continuous training, reverses right ventricular hypertrophy and dysfunction in a rat model of pulmonary hypertension. Am J Physiol Regul Integr Comp Physiol. 2017;312:R197–210. https://doi.org/10.1152/ajpregu.00358.2016
109. Spruijt OA, de Man FS, Groepenhoff H, Oosterveer F, Westerhof N, Vonk-Noordegraaf A, Bogaard HJ. The effects of exercise on right ventricular contractility and right ventricular-arterial coupling in pulmonary hypertension. Am J Respir Crit Care Med. 2015;191:1050–7. https://doi.org/10.1164/rccm.201412-2271OC
110. Singh I, Oliveira RKF, Heerdt P, Brown MB, Faria-Urbina M, Waxman AB, Systrom DM. Dynamic right ventricular function response to incremental exercise in pulmonary hypertension. Pulm Circ. 2020;10:1–8. https://doi.org/10.1177/2045894020950187
111. Sadowska O, Baranowska-Kuczko M, Gromotowicz-Popławska A, Biernacki M, Kicman A, Malinowska B, Kasacka I, Krzyżewska A, Kozłowska H. Cannabidiol ameliorates monocrotaline-induced pulmonary hypertension in rats. Int J Mol Sci. 2020;21:7077. https://doi.org/10.3390/ijms21197077
112. Lu X, Zhang J, Liu H, Ma W, Yu L, Tan X, Wang S, Ren F, Li X, Li X. Cannabidiol attenuates pulmonary arterial hypertension by improving vascular smooth muscle cells mitochondrial function. Theranostics. 2021;11:5267–78. https://doi.org/10.7150/thno.55571
113. Kozłowska H, Baranowska M, Schlicker E, Kozłowski M, Laudañski J, Malinowska B. Virodhamine relaxes the human pulmonary artery through the endothelial cannabinoid receptor and indirectly through a COX product. Br J Pharmacol. 2008;155:1034–42. https://doi.org/10.1038/bjp.2008.371
114. Consumer Brands Association. Unregulated and exploding: how the CBD market is growing amid a labyrinth of state approaches and rampant consumer confusion. Consumer Brands Association; 2021. https://consumerbrandsassociation.org/regulation/cbd/unregulated-and-exploding-how-the-cbd-market-is-growing-amid-a-labyrinth-of-state-approaches-and-rampant-consumer-confusion/
115. Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R. Labeling accuracy of cannabidiol extracts sold online. JAMA. 2017;318:1708–9. https://doi.org/10.1001/jama.2017.11909
116. Yoshifuku S, Otsuji Y, Takasaki K, Yuge K, Kisanuki A, Toyonaga K, Lee S, Murayama T, Nakashima H, Kumanohoso T, Minagoe S, Tei C. Pseudonormalized Doppler total ejection isovolume (Tei) index in patients with right ventricular acute myocardial infarction. Am J Cardiol. 2003;91:527–31.
117. Combes A, Price S, Slutsky AS, Brodie D. Temporary circulatory support for cardiogenic shock. Lancet. 2020;396:199–212. https://doi.org/10.1016/s0140-6736(20)31047-3
118. Burkhoff D, Sayer G, Doshi D, Uriel N. Hemodynamics of mechanical circulatory support. J Am Coll Cardiol. 2015;66:2663–74. https://doi.org/10.1016/j.jacc.2015.10.017
119. Montisci A, Maj G, Zangrillo A, Winterton D, Pappalardo F. Management of refractory hypoxemia during venovenous extracorporeal membrane oxygenation for ARDS. ASAIO J. 2015;61:227–36. https://doi.org/10.1097/mat.0000000000000207
120. Downey P, Ragalie W, Gudzenko V, Ardehali A. Ambulatory central veno-arterial extracorporeal membrane oxygenation in lung transplant candidates. J Heart Lung Transplant. 2019;38:1317–9. https://doi.org/10.1016/j.healun.2019.09.006
121. Hakim AH, Ahmad U, McCurry KR, Johnston DR, Pettersson GB, Budev M, Murthy S, Blackstone EH, Tong MZ. Contemporary outcomes of extracorporeal membrane oxygenation used as bridge to lung transplantation. Ann Thorac Surg. 2018;106:192–8. https://doi.org/10.1016/j.athoracsur.2018.02.036
122. Biscotti M, Gannon WD, Agerstrand C, Abrams D, Sonett J, Brodie D, Bacchetta M. Awake extracorporeal membrane oxygenation as bridge to lung transplantation: a 9-year experience. Ann Thorac Surg. 2017;104:412–9. https://doi.org/10.1016/j.athoracsur.2016.11.056
123. Nam KH, Koh Y, Lim C-M, Huh JW, Jung SH, Kang PJ, Lim JY, Hong SB. Central extracorporeal membrane oxygenation for bridging of right-sided heart failure to lung transplantation: a single-center experience and literature review. J Cardiothorac Vasc Anesth. 2019;33:1873–6. https://doi.org/10.1053/j.jvca.2019.01.059
124. Punnoose L, Burkhoff D, Rich S, Horn EM. Right ventricular assist device in end-stage pulmonary arterial hypertension: insights from a computational model of the cardiovascular system. Prog Cardiovasc Dis. 2012;55:234–43.e2. https://doi.org/10.1016/j.pcad.2012.07.008
125. Cain MT, Smith NJ, Barash M, Simpson P, Durham LA, Makker H, Roberts C, Falcucci O, Wang D, Walker R, Ahmed G, Brown SA, Nanchal RS, Joyce DL. Extracorporeal membrane oxygenation with right ventricular assist device for COVID-19 ARDS. J Surg Res. 2021;264:81–9. https://doi.org/10.1016/j.jss.2021.03.017
126. Usman AA, Spelde AE, Ibrahim M, Cevasco M, Bermudez C, MacKay E, Khandhar S, Szeto W, Vernick W, Gutsche J.

Comprehensive monitoring in patients with dual lumen right atrium to pulmonary artery right ventricular assist device. ASAIO J. 2022;68:1461–9. https://doi.org/10.1097/mat.0000000000001684

127. Kapur NK, Paruchuri V, Jagannathan A, Steinberg D, Chakrabarti AK, Pinto D, Aghili N, Najjar S, Finley J, Orr NM, Tempelhof M, Mudd JO, Kiernan MS, Pham DT, DeNofrio D. Mechanical circulatory support for right ventricular failure. JACC Heart Fail. 2013;1:127–34. https://doi.org/10.1016/j.jchf.2013.01.007
128. Javidfar J, Brodie D, Sonett J, Bacchetta M. Venovenous extracorporeal membrane oxygenation using a single cannula in patients with pulmonary hypertension and atrial septal defects. J Thorac Cardiovasc Surg. 2012;143:982–4. https://doi.org/10.1016/j.jtcvs.2011.10.061
129. Rosenzweig EB, Chicotka S, Bacchetta M. Right ventricular assist device use in ventricular failure due to pulmonary arterial hypertension: lessons learned. J Heart Lung Transplant. 2016;35:1272–4. https://doi.org/10.1016/j.healun.2016.07.010
130. Reitz BA, Wallwork JL, Hunt SA, Pennock JL, Billingham ME, Oyer PE, Stinson EB, Shumway NE. Heart-lung transplantation: successful therapy for patients with pulmonary vascular disease. N Engl J Med. 1982;306:557–64. https://doi.org/10.1056/nejm198203113061001
131. Chambers DC, Cherikh WS, Harhay MO, Hayes D, Hsich E, Khush KK, Meiser B, Potena L, Rossano JW, Toll AE, Singh TP, Sadavarte A, Zuckermann A, Stehlik J. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth Adult Lung and Heart-lung Transplantation Report-2019; focus theme: donor and recipient size match. J Heart Lung Transplant. 2019;38:1042–55. https://doi.org/10.1016/j.healun.2019.08.001
132. Khush KK, Cherikh WS, Chambers DC, Goldfarb S, Hayes D, Kucheryavaya AY, Levvey BJ, Meiser B, Rossano JW, Stehlik J. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-fifth Adult Heart Transplantation Report-2018; focus theme: multiorgan transplantation. J Heart Lung Transplant. 2018;37:1155–68. https://doi.org/10.1016/j.healun.2018.07.022
133. Leard LE, Holm AM, Valapour M, Glanville AR, Attawar S, Aversa M, Campos SV, Christon LM, Cypel M, Dellgren G, Hartwig MG, Kapnadak SG, Kolaitis NA, Kotloff RM, Patterson CM, Shlobin OA, Smith PJ, Solé A, Solomon M, Weill D, Wijsenbeek MS, Willemse BWM, Arcasoy SM, Ramos KJ. Consensus document for the selection of lung transplant candidates: an update from the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2021;40:1349–79. https://doi.org/10.1016/j.healun.2021.07.005
134. Porteous MK, Ky B, Kirkpatrick JN, Shinohara R, Diamond JM, Shah RJ, Lee JC, Christie JD, Kawut SM. Diastolic dysfunction increases the risk of primary graft dysfunction after lung transplant. Am J Respir Crit Care Med. 2016;193:1392–400. https://doi.org/10.1164/rccm.201508-1522OC
135. Hoeper MM, Behr J, Held M, Grunig E, Vizza CD, Vonk-Noordegraaf A, Lange TJ, Claussen M, Grohé C, Klose H, Olsson KM, Zelniker T, Neurohr C, Distler O, Wirtz H, Opitz C, Huscher D, Pittrow D, Gibbs JSR. Pulmonary hypertension in patients with chronic fibrosing idiopathic interstitial pneumonias. PLoS One. 2015;10:e0141911. https://doi.org/10.1371/journal.pone.0141911

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