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REVIEW

Pharmacotherapy

Shifting Paradigms in the Management of Pulmonary Hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is a long-term condition characterised by increased resistance to blood flow in the pulmonary circulation. The disease has a progressive course and is associated with a poor prognosis. Without treatment, PAH is associated with mortality in <3 years. Over the past decade, many advances have been made in revising the haemodynamic definition, clinical classification, risk calculation score, treatment options etc. Suggestions from the Sixth World Symposium on Pulmonary Hypertension were incorporated into a literature review that was included in the European Society of Cardiology/European Respiratory Society (ESC/ERS)'s most recent iteration of their guidelines in 2022. The traditional cut-off for pulmonary hypertension (PH), i.e., mean pulmonary artery pressure (mPAP) >25 mm Hg, has been challenged by observational cohort studies, which have shown poor outcomes for values of 21–24 mmHg; the new consensus is that PH is defined at mPAP >20 mm Hg. Although the gold standard for diagnosis and the major source of therapy guidance continues to be right cardiac catheterisation, echocardiography remains the initial test of choice. A multidisciplinary approach is highly recommended when treating PH patients and careful evaluation of patients will aid in proper diagnosis and prognosis. Pharmacotherapy for PAH has seen a paradigm shift with the successful use of newer agents in more extensive, longer and more inclusive trials driven by hard endpoints. Macitentan, selexipag and riociguat are three oral agents that have shown astounding success in PAH randomised studies in the past decade. Upfront combination therapy with two agents is now becoming the norm (following the AMBITION, OPTIMA and ITALY trials) and the momentum is shifting towards triple therapy as for essential hypertension. More recently, inhaled treprostinil was shown to improve exercise capacity in PH associated with interstitial lung disease in the phase III INCREASE study and has been granted regulatory approval for World Health Organization group 3 PH. A new class of drug, sotatercept (a tumour growth factor-β signalling inhibitor), has also been recently approved by the Food and Drug Administration for management of PAH based on positive results from the phase III STELLAR study. Pulmonary artery denervation and balloon pulmonary angioplasty have emerged as viable alternatives in PH that are resistant to drug therapy. This article aims to summarise the key changes and recent advances in diagnosis and managing PH in general, with an emphasis on certain subgroups.

Keywords

Definition, REVEAL 2.0, upfront combination therapy, selexipag, riociguat, balloon pulmonary angioplasty

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Pulmonary circulation was described for the first time by Ibn al-Nafis during the 13th century. William Harvey provided a more detailed description in the 1600s in his publication *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* and proposed that blood flowed in two separate closed parallel loops through the two sides of the heart. He also discarded Galen's previous view that direct communication existed between right and left ventricles and, instead, believed that the blood from the vena cava passes via the right side of the heart to porous tissue of the lungs and thereafter to the aorta.[1,2] It took several centuries and multiple anatomists, physicians and surgeons to refine the understanding of pulmonary circulation as it is today.

Gradually, the association of sclerosis of the pulmonary artery with pulmonary artery thrombus and parenchymal lung diseases became established. In 1891, Ernst von Romberg described the morphological changes in the vessels as "über Sklerose den Lungenarterie" (over sclerosis of the pulmonary artery).[3–5] The histopathologic characteristics, clinical association and high mortality rates became better defined.

The first World Symposium on Pulmonary Hypertension was organised by the WHO in 1973. This was held after the pulmonary hypertension epidemic caused by the anorexic agent aminorex fumarate.[6,7] Until then, primary pulmonary hypertension (PH) and secondary PH were the major categories. The haemodynamic definition was given as mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest measured by right heart catheterisation (RHC).[6,7] The status of PH changed from being a rare and fatal disease to one requiring more studies to understand causation.

The need for therapeutic advancement was recognised. By the time the second symposium was held in France in 1998, knowledge had increased in every aspect of the disease, and a diagnostic classification comprising five classes was proposed (*Table 1*).[8,9] The third symposium was held in

Table 1: Classification of Pulmonary Hypertension by World Symposia

Class	Clinical Classification of the Second World Symposium on PH[7,8]	Original Danapoint Classification of the Fourth World Symposium on PH[8,9]	Latest Clinical Classification of the Sixth World Symposium on PH[11]
I	PAH	PAH	PAH
II	PVH	PH associated with left heart diseases	PH due to left heart disease
III	PH associated with disorders of respiratory system and/or hypoxaemia	PH associated with lung diseases and/or hypoxaemia	PH due to lung diseases and/or hypoxia
IV	PH due to chronic thrombotic and/or embolic disease	PH owing to chronic thrombotic and/or embolic disease	PH due to pulmonary artery obstructions
V	PH due to disorders directly affecting the pulmonary vasculature	Miscellaneous	PH due to unclear/multifactorial mechanisms

PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; PVH = pulmonary venous hypertension.

Italy in 2003, where more insights were gained into the pathogenesis, including identifying genetic mutations associated with familial and idiopathic PH. An algorithm for treatment was developed for the first time. It was proposed to abandon the term primary PH in favour of idiopathic PH.[8,9] The Danapoint classification and an update of the treatment algorithm marked the fourth symposium in 2008.[9,10] The fifth symposium in 2013 highlighted that WHO groups 1 and 5 PH had been slightly modified and new responsible mutations identified.[11] Meanwhile, the need for early diagnosis and treatment became increasingly acknowledged over time. The Sixth World Symposium on Pulmonary Hypertension in 2018 was a new milestone as it provided a new haemodynamic definition of PH, setting the threshold of mPAP at >20 mmHg measured by RHC.[12] Major modifications and advances in the field of PH since are detailed below.

Changes in Definition and Classification

For a long time, it has been known that normal mPAP seldom rises above 15 mmHg. A systematic review by Kovacs et al. in 2009 concluded that the average normal mPAP has a range of 14 ± 3.3 mmHg.[13,14] Hence, an mPAP of 20–25 mmHg was always viewed with suspicion. However, ample new evidence shows that individuals with an mPAP of 20–25 mmHg are at greater risk of morbidity and development of PH.[15–17] Therefore, PH was redefined as mPAP >20 mmHg assessed by RHC at rest.[18] Moreover, it was repeatedly emphasised throughout the proceedings of the sixth symposium that the mere presence of raised mPAP is not adequate to confirm PH. There must be a concomitant elevation of pulmonary vascular resistance (PVR) of >2 Woods units (WU) to identify pre-capillary PH.[12] Pulmonary arterial wedge pressure (PAWP) of ≤15 mmHg is already used to distinguish pre-capillary from post-capillary and combined aetiology.

Exercise-induced PH or exercise PH was previously defined as mPAP of >30 mm Hg. This has given way to the new definition based on ratio of mPAP to cardiac output (CO). The European Society of Cardiology (ESC) and European Respiratory Society (ERS) 2022 guideline defined this as an mPAP/CO slope >3 mm Hg/l/min.[18] However, the values are age dependent, and this definition fails to differentiate between pre-capillary and post-capillary forms of PH. Nevertheless, a high mPAP/CO slope predicts worse outcomes in patients with chronic dyspnea.[19]

Modifications have been made to the clinical classification as well. The five groups of this have repeatedly undergone modification in light of new evidence (*Table 1*). For the update of group 1, at the Sixth World Symposium on Pulmonary Hypertension it was proposed to further subclassify drug- and toxin-induced PH into definite association and possible association categories.[12] Aminorex and fenfluramines were already known to be causative; there is now evidence supporting a definite association of amphetamines and dasatanib with PH as well.[20–23] Other agents with limited evidence have been placed under possible associations.[24,25] The erstwhile 1 ' group of pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis has been categorised as subgroup 1.6 as pulmonary arterial hypertension with overt features of venous/capillary involvement.[12]

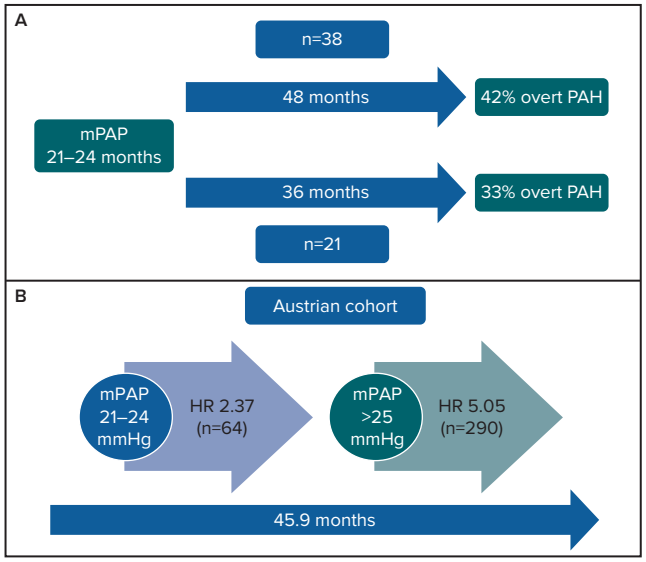
Group 2 comprises of PH that develops due to left heart disease and involves the mechanism of elevated left atrial pressure contributing to passive venous congestion in the pulmonary circulation and is characterised by PAWP>15 mmHg. Here, there has been recognition of heart failure with preserved ejection fraction, and thus the subgroups have been refined. It is recommended to calculate pretest probability before invasive confirmation of left heart disease. Within group 2, isolated and combined post-capillary PH may be differentiated by haemodynamic characterisation.[12,26–28]

In the third clinical group, the nomenclature of the first two subgroups has been modified from chronic obstructive pulmonary disease and interstitial lung disease to more comprehensive terms: obstructive and restrictive lung disease, respectively. Sleep-related hypoventilation and high-altitude disorders have been included in a broad subclass of hypoxia without lung disease. The fact that lung diseases further worsen the prognosis of PH has been acknowledged again.[12,29]

Group 4, confined to chronic thromboembolic PH (CTEPH), now encompasses several causes of pulmonary artery obstruction, including malignant and non-malignant tumours, arteritis without connective tissue disease, congenital pulmonary artery stenosis and hydatidosis as well. The new 2022 PH guidelines have described a new category of chronic thromboembolic pulmonary disease (CTEPD) with or without PH.[18] This acknowledges the presence of a group with proven CTEPD with mPAP values below the diagnostic threshold leading to limitations in functional class and quality of life. Yet the mPAP values preclude any therapy and such patients cannot take part in clinical trials. Recently, improvements in haemodynamic parameters, 6-minute walk distance (6MWD) and functional class have been demonstrated after surgery in this group.[30] Thus, the new haemodynamic definition applies to both CTEPH and chronic thromboembolic disease where PH is absent at rest.[12,31]

Group 5 has been renamed PH with unclear and/or multifactorial mechanisms. This is apt as further study is required to identify most conditions in this category. These and metabolic disorder subgroups have been combined into one, and complex congenital heart diseases have been added as a new subgroup.

Figure 1: Outcomes in Patients with Borderline Pulmonary Hypertension (mPAP 21–24 mm Hg) in Various Observational Studies



A: The proportion of borderline patients developing overt pulmonary hypertension during follow-up. The upper arrow depicts the UK cohort by Valerio et al. while the lower arrow refers to the mixed cohort from the UK and Germany by Coghlan et al.[15,16] B: Adverse outcomes on follow up in patients with borderline pulmonary hypertension in the Austrian cohort by paper Douschan et al.[17] mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension.

Splenectomy and thyroid disorders still lack a strong causative relation with PH and have been removed. Both these conditions, however, are common comorbidities that need to be addressed alongside PH management.[12,32]

Advances in Diagnosis

The previous guidelines by the ESC joint task force and the ERS recommended clinical presentation and echocardiography for diagnosis.[33,34] However, in patients in whom the underlying disease mimics the symptoms and signs of PH, as occurs in connective tissue disorders or lung diseases, the diagnosis of PH gets delayed with over-reliance on clinical presentation.[35–38]

A successful attempt to address this issue was made by Coghlan et al. in the DETECT study in 2014 by developing an algorithm for PH screening in patients with systemic sclerosis (SSc).[39] The first step of this algorithm uses telangiectasia, anti-centromere antibody, a ratio of forced vital capacity to diffusion capacity <1.6, serum urate level, serum N-terminal brain natriuretic peptide (NT-proBNP) and right axis deviation on the electrocardiogram. The total score of step 1 determines the need for the second step, which includes assessing tricuspid regurgitation velocity and the right atrial size. The combined points from the two scores are used to refer a patient for RHC. This algorithm has a high sensitivity to detect mild cases of PH in SSc. The 2015 ESC/ERS guideline recommends screening for PH via echocardiography in asymptomatic SSc cases and mentions the DETECT study.[33,39]

Twenty is the New 25

As explained previously, the mPAP value of >25 mm Hg for pulmonary arterial hypertension (PAH) definition was an arbitrary cut-off by consensus. A large (n=1,187) and RHC-based study by Kovacs et al. in healthy adults reported the mPAP to be centred around 14 ± 3.3 mmHg.[13] This figure was found to apply regardless of ethnicity and sex, lending further credibility. So, taking two standard deviations into consideration, the ideal cut-off for PAH should be somewhere around 20 mm Hg.[40] However, clinical data to support this hypothesis were lacking.

Two cohort studies in SSc with borderline elevated mPAP (21–24 mm Hg) have made revelations regarding the outcomes of this subset, hitherto believed to be benign (*Figure 1*).

Valerio et al. studied 86 patients with SSc with an mPAP of 21–24 mm Hg (on RHC) for 48 ± 35 months.[15] At follow-up, 16 patients (42%) developed overt PAH (mPAP >25) and the mean mPAP rose to 31 ± 6 mm Hg. Simultaneously, PVR was elevated to 6.9 ± 1.7 WU from a baseline of 2.9 ± 0.6 WU. The HR for developing overt PAH in patients with borderline mPAP was 3.72 (p<0.01) with 18% mortality at 3 years.

Coghlan et al. similarly followed 21 subjects with SSc with borderline mPAP (21–24 mm Hg on RHC) for 3 years.[16] One-third (33%) of patients developed overt PAH (RHC confirmed) during the study. Compared to the group with mPAP <20, the borderline PAH had a significantly higher risk of developing overt PAH.

Douschan et al. examined a series of 547 patients with unexplained dyspnoea and/or at risk of PH who underwent RHC. Manifest PH (mPAP ≥25 mmHg) was confirmed in 290 patients, borderline PH (mPAP 21–24 mmHg) in 64 cases, and 193 cases were considered as normal with an mPAP ≤20 mmHg; of these, 137 were defined as lower normal with an mPAP ≤15 mmHg.[17] The median follow-up time of this cohort was 45.9 months; overall, 161 patients (29%) died during the follow-up period. In the multivariate model, considering age and comorbidities, both borderline PH and manifest PH were significantly associated with poor survival compared with the lower normal group. (*Figure 1*)

Risk Stratification: REVEAL 2.0 and beyond

The lethal nature of PH led investigators to identify factors that can predict survival. Different PH registries were analysed from time to time and algorithms were developed.

The first algorithm was derived from the National Institutes of Health registry in 1991, which considered demographic, haemodynamic, gas exchange and pulmonary function variables.[41] Following that was REVEAL, a landmark US-based multicentre study in which over 3,000 participants were followed up for 5 years.[42] These participants included group 1 PH patients. Their demographics, disease course and outcomes were studied. It was concluded that New York Heart Association (NYHA) functional class (FC) is the best predictor of a worse outcome as most participants had NYHA FC III or IV when they were diagnosed with PH by RHC. A risk calculator score predicting mortality was developed using variables that best predicted the outcome based on an equation with a c-index of 0.72 [95% CI]. This equation can be applied to diverse population groups and used repeatedly in the follow-up of a patient. Other algorithms were derived later, including Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), Swedish Pulmonary Arterial Hypertension Register (SPAHR) and French Pulmonary Hypertension Registry (FPHR).[43–45]

To improve the predictive power of the REVEAL risk score calculator, an updated version was developed and published in 2018: REVEAL 2.0.[46] While the original REVEAL risk score had assigned a score of 2 to PoPH (portopulmonary hypertension), the latest score allocates 3 points. The comorbidity variable has been refined to include estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2; renal insufficiency may be

Table 2: Summary of Modifications to the Original REVEAL Risk Score

Variable	Modification in Variable	Modification in Points
Demographics	None	None
Echocardiogram	None	None
WHO group 1 subgroup	None	Revised: +3 to PoPH
NYHA/WHO class	None	Revised: −1 to functional class I
Comorbidities	Revised: eGFR <60 ml/min/1.73 m^2	None
Vital signs	Revised: heart rate >96 BPM	None
BNP	Revised: <50 pg/ml or NT-proBNP <300 pg/ml 200–800 pg/ml ≥800 pg/ml or NT-proBNP >1,100 pg/ml	Revised: −2 +1 +2
PFT	Revised: DLCO% predicted <40%	+1
6MWD	Revised: ≥440 m 320–440 m <165 m	Revised: −2 −1 +1
Right heart catheterisation	Revised: PVR <5 Woods units	Revised: −1
All-cause hospitalisations within 6 months	Newly added	+1

DLCO = diffusion capacity of the lungs for carbon monoxide; eGFR = estimated glomerular filtration rate; NT-proBNP = N terminal brain natriuretic peptide; NYHA = New York Heart Association; PFT=pulmonary function test; PoPH = portopulmonary hypertension; PVR = pulmonary vascular resistance.

considered if eGFR is not available. The set value of this variable remains the same at 1 point. The FC I score of disability assessed by either NYHA or WHO classification has changed incrementally from −2 to −1. In contrast, a 6MWD of ≥440 m has declined in score from −1 to −2; a new category of 320–440 m has been added and assigned −1 point. Among the vital signs, the cut-off for heart rate has risen from >92 to >96 beats per minute.

Brain natriuretic peptide (BNP) has undergone revised categorisation and scores updated: BNP <50 pg/ml or NT-proBNP <300 pg/ml gets −2 points, BNP 200 pg/ml to <800 pg/ml gets +1 point, and BNP ≥800 pg/ml or NT–proBNP ≥1,100 pg/ml gets a score of +2. The scoring of pulmonary function test has been simplified to a single cut-off of diffusion capacity of the lungs for carbon monoxide of <40% and given a point of +1.

Under the variable of RHC, the PVR point has undergone a major modification from being a positive score in case of higher resistance (PVR >32 WU) to a negative score value of −1 if PVR is <5 WU.

Finally, a new variable has been added: if the patient has been hospitalised within 6 months due to any cause, 1 point is added to the score. Demography and echocardiography variables remain unchanged.
The changes are summarised below in *Table 2*.

The risk calculator has proven to be at par with the original REVEAL risk score and better than the COMPERA and French Pulmonary Hypertension Registry risk assessment strategy. The utility in predicting short-term and long-term outcomes has been proven in the PATENT-1 and PATENT-2 studies.[47,48] Another simplified version of REVEAL was later developed using only six non-invasive variables and was named REVEAL LITE (*Supplementary Table 1*).[49]

Risk assessment was based on a multiparametric method in the 2022 ESC/ERS guidelines for diagnosing and managing PH, employing a four-stratum model to categorise patients as having a low, intermediate low, intermediate high or high risk of death. This four-stratum classification was long overdue owing to the large size of the intermediate risk group, which encompasses >60% patients (*Supplementary Table 2*). It was demonstrated that the four-strata model's mortality prediction abilities were at least on par with those of the three-strata model. Patients with PoPH, idiopathic PAH (IPAH), hereditary PAH (HPAH), drug-induced PAH (DPAH) and PAH linked with connective tissue disease (CTD) (including the SSc subgroup) were projected to survive in the four-strata model. The observed 1-year death rates in the four risk strata were, respectively, 0–3%, 2–7%, 9–19%, and >20%.[50]

The guidelines recommend the use of the three-strata model at diagnosis and the four-strata model at follow-up. The updated risk calculators, such as COMPERA 2.0 and updated SPAHR, have demonstrated the different prognostic significance of intermediate–low-risk and intermediate–high-risk groups. While the intermediate–low-risk group can convert to low risk on follow-up, this is unlikely in the intermediate–high-risk group.[51,52] The novel risk calculators have also been simplified to rely solely on non-invasive variables and allow more widespread use (*Supplementary Table 1*).

Among other options for risk stratification, serum biomarkers BNP and NT-proBNP have stood the test of time.[50,53] In 2017, Rhodes et al. identified 20 new biomarkers that differentiate between survivors and non-survivors in the 2-year follow-up.[54] Nine proteins are of special mention as they could predict PH with higher mortality risk independent of serum NT-proBNP levels. These include complement factors H and D, tissue inhibitors of metalloproteinases 1 and 2, interleukin-1 receptor-like 1, erythropoietin, apolipoprotein E, plasminogen and insulin-like growth factor binding protein-1.[54] While these markers offer an unbiased and confounding-proof prognostication, they could also be used in future research on targeted therapies.

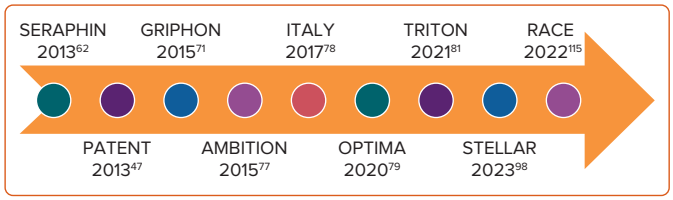
Cardiac MRI has gained importance as a sensitive, non-invasive modality to assess the morphology and function of the right ventricle and pulmonary vasculature. It overcomes the operator bias of the echocardiography.[55,56]

Medical Management: Large-scale Trials

Until 1998, the management options of PH were confined to calcium channel blockers (CCBs), prostaglandins and lung transplant.[3,4] By the third symposium in 2003, treatment algorithms involving seven drugs had been developed.[8,9]

Currently, more than 10 drugs are approved for the medical management of PAH and CTEPH. These include: selective and non-selective endothelin receptor antagonists (ERAs) – ambrisentan, bosentan and macitentan; those targeting nitric oxide pathway – phosphodiesterase-5 (PDE-5) inhibitors sildenafil and tadalafil; a soluble guanylate cyclase stimulator – riociguat; and some of the oldest group of drugs that were identified to reduce mortality in this progressive disease – prostanoids, such as iloprost, treprostinil and epoprostenol, and oral prostaglandin receptor agonist selexipag.[12,33]

Figure 2: Recent Trials



Timeline of different trials in the pharmacological management of pulmonary hypertension in the past decade.

Figure 2 summarises the landmark trials in pharmacotherapy for PH in the past decade.

Traditional Monotherapy – On the Way Out!

Traditionally, monotherapy with agents targeting one of three pathogenic pathways of PH viz. endothelin system, nitrous oxide system and prostacyclin system have been the standard of care. However, upfront combination therapy and molecules targeting novel pathogenic targets (TGF-β signalling) are the newfangled approaches in the pharmacotherapy of PH.

Calcium Channel Blockers

These are recommended as class I drugs where there is a positive response on vasoreactivity testing. Recommended CCBs include nifedipine, diltiazem and amlodipine. If an adequate response is not seen and the patient is in the WHO FC 3/4, additional PAH-specific therapy is advised.[57]

Endothelin Receptor Antagonists

These include selective and non-selective ERAs, such as ambrisentan, bosentan and macitentan, and those targeting the nitric oxide pathway, such as PDE-5 inhibitors sildenafil and tadalafil. Endothelin-1 causes vasoconstriction and mitogenic effects by binding to endothelin receptor types A and B. Ambrisentan binds to endothelin receptor type A and inhibits it. It was shown to improve exercise capacity, WHO FC, time to clinical worsening and BNP in ARIEs-1 and -2 studies.[58] It is given at a dose of 2.5 mg, 5 mg or 10 mg orally once a day. Side effects include minimal elevation of aminotransferases and pedal oedema.

Bosentan is an endothelin receptor type A and B antagonist given orally at a dosage of 62.5 mg twice a day. It has been evaluated for its efficacy in randomised control trials (RCTs) BREATHE-1, BREATHE-2, BREATHE-5, EARLY and COMPASS 2.[59–61] Bosentan has shown to improve exercise capacity, WHO FC, haemodynamics, echocardiographic and Doppler variables and time to clinical deterioration. Side effects include elevation of aminotransferases (10% of patients).

Macitentan is endothelin receptor type A and B antagonist and administered orally at a dosage of 10 mg once daily. It was evaluated in the SERAPHIN trial and was shown to reduce morbidity and mortality and increase exercise capacity. Side effects include headache, nasopharyngitis and anaemia. The SERAPHIN trial was the largest trial in the study of endothelin receptor antagonists to assess long-term outcomes.[62] It was a Phase III, double-blind, randomised study in which a total of 742 PAH patients of WHO FC class 2, 3 or 4 were recruited, of whom two groups of 250 each were given a placebo and 3 mg macitentan and the remaining 242 receiving 10 mg macitentan. The median duration of follow-up was 129 weeks. The patients were allowed to continue their ongoing treatment with CCBs, L-arginine, PDE-5-inhibitors or oral or inhaled prostaglandins. The primary endpoint was defined by PAH worsening, atrial septostomy, lung transplant, use of injectable prostanoids or death. Macitentan significantly reduced the risk of primary outcomes and the effects were more pronounced with the higher dose (10 mg). The drug was well tolerated, which established the long-term safety of macitentan as well as its effectiveness as a combination agent.

Phosphodiesterase-5 Inhibitors

PDE-5 inhibitors act by inhibiting cGMP, degrading PDE-5 and leading to vasodilation through the nitric oxide/cGMP pathway at sites expressing this enzyme. Pulmonary vasculature has a high amount of the PDE-5 enzyme. Sildenafil is an oral PDE-5 inhibitor given at a dosage of 20 mg 8 hourly. Sildenafil efficacy was evaluated in patients with PAH in the SUPER trial.[63] It showed that its use improves exercise capacity, 6MWD and WHO FC, and reduces mPAP.

Tadalafil is an oral PDE-5 inhibitor given at a dose of 2.5–40 mg once a day. Its efficacy was evaluated in patients with PAH in the PHIRST trial.[64] This showed that it improves exercise capacity, 6MWD, time to clinical worsening and health-related quality of life.

Vardenafil is an oral PDE-5 inhibitor given at a dosage of 5 mg twice daily. Its efficacy was assessed in patients of PAH in the EVALUATION trial.[65] The study revealed it improves 6MWD and cardiac index, and decreases mPAP and PVR. The side effects of the drug include headache, flushing and myalgias.

Prostacyclin Analogues

Prostacyclin is produced by endothelial cells. It induces vasodilation of all vascular beds and has cytoprotective and antiproliferative action. In patients with PAH, there is dysregulation of the prostacyclin metabolic pathway and decreased prostacyclin synthase expression in pulmonary arteries.

Beraprost was the first orally active prostacyclin analogue evaluated for its role in patients with PAH in a beraprost study group at a median dose of 120 µg four times a day.[66] It showed improvement in 6MWD and decreased evidence of disease progression during the early phase of treatment. Side effects included headache, flushing, jaw pain and diarrhoea.

Epoprostenol is a prostacyclin analogue administered via an infusion pump at a starting dose of 2–4 ng/kg/min with an optimal dose of 20–40 ng/kg/min. Increasing the dose is limited by side effects, such as flushing, headache, diarrhoea and leg pain. The efficacy of epoprostenol has been evaluated in RCTs, which showed improvements in exercise capacity, 6MWD, quality of life, mPAP and PVR. There were also side effects related to delivery system complications, such as pump malfunction, local site infection, catheter obstruction and sepsis. To avoid rebound PH, abrupt interruption of epoprostenol infusion is avoided.[67]

Iloprost is a prostacyclin analogue available in IV, oral and inhalational administration forms. Inhalational iloprost was evaluated in the Aerosolized Iloprost Randomized Study Group at a dose of 2.5–5 µg per inhalation with 30 µg daily. It improved 6MWD, NYHA class, quality of life, haemodynamic parameters. Side effects included flushing and jaw pain.

Treprostinil is a prostacyclin analogue available for IV, inhaled, oral and subcutaneous administration. Subcutaneous treprostinil was shown to improve 6MWD, indices of dyspnoea, signs and symptoms of PH, and

haemodynamics. It is started at a dose of 1–2 ng/kg/min with an optimal dosage of 20–80 ng/kg/min. Side effects, such as flushing and headache, limit dosage increases. The inhaled form has also demonstrated greater improvements in 6MWD, NT-proBNP and quality of life in PH patients than baseline PH therapy. Based on the positive data from TRIUMPH study, the inhalation solution was approved for use in PAH.[68] Oral treprostinil has been evaluated in two FREEDOM-C RCTs, which enrolled patients with background PH therapy.[69] The oral form of drug failed to improve 6MWD in both trials. However, the drug improved 6MWD as a monotherapy in treatment-naïve patients. More recently, the drug improved worsening clinical events (by 24%) when used as monotherapy. Concomitantly, NT-pro BNP, functional class and Borg dyspnoea score were also improved.

Although inhaled treprostinil therapy was approved in 2009, using it remains onerous owing to need for a nebuliser for drug delivery and multiple administrations in a day. More recently, an easy-to-use dry powder inhalation (DPI) form of treprostinil has been tried in group 1 PH. This single-use, cartridge-based inhaler device is patient-friendly with the potential to improve compliance. In the BREEZE trial, 51 patients with PAH on inhaled treprostinil solution were moved to this treprostinil DPI.[70] At 3 weeks, there was significant improvement in 6 MWD, patient satisfaction scores and PAH symptom scores. More patients preferred the DPI device based on a structured questionnaire; fewer inhalations were required with the new DPI device indicating effective drug delivery to the lungs. The improvements in 6MWD were sustained in open label extension (OLE) of the study until 52 weeks. The Food and Drug Administration (FDA) granted approval for treprostinil powder-based DPI for use in group 1 PH or PAH in May 2022.

Prostacyclin Receptor Agonist

Selexipag is an oral prostacyclin receptor agonist given at 1,600 µg twice daily. The drug is structurally and pharmacologically different from prostacyclin but exhibits a selectively high affinity for prostacyclin receptors. Side effects of the drug include headache, diarrhoea, nausea and jaw pain.

The GRIPHON study was a Phase III, double-blind, randomised trial which included 1,156 subjects with group 1 PH.[71] Those already receiving treatment in the form of ERA or PDE-5 inhibitors could take part. Of the participants, 582 received placebo while 574 were initiated on selexipag. The primary endpoint was a complication, such as disease worsening, parenteral prostanoid treatment, long-term oxygen therapy, atrial septostomy, lung transplant or death. Three different maintenance doses were provided to the subgroups of the selexipag arm. The HR for the primary endpoint with selexipag was 0.60, which was significant. The different doses demonstrated similar efficacy and the drug was found to be safe with other agents. Mortality did not vary between the two groups. Selexipag reduced the combined primary endpoint of death from any cause or complication of PH by 40% at 70 weeks. This was driven primarily by slowed disease progression and lower hospitalisation rates.

The SERAPHIN and GRIPHON studies marked a new era in PH studies. These studies were larger in size and had a longer follow-up. They also included patients with other background PH therapy, unlike previous studies, simulating real-world clinical practice. The inclusion of varied aetiologies of PAH, such as that due to connective tissue disorders, congenital diseases, toxins, HIV or drugs was a stark departure from previous studies which usually enrolled only iPAH patients, and implication is a wider generalisability of these results. Furthermore, the use of clinical endpoints in these studies has taken PAH therapy utility beyond the realms of palliative care to a disease-modifying era, impacting both mortality and quality of life.

Soluble Guanylate Cyclase Stimulator

Riociguat is a soluble guanylate cyclase stimulator enhancing cGMP production. The drug not only directly stimulates guanylate cyclase independent of nitric oxide (NO) but also increases the sensitivity of guanylate cyclase to NO. It is given orally at a dosage of 1.0–2.5 mg three times a day.[72] So far, these drugs have not proven to be effective in other classes of PH other than CTEPH. In fact, it is the only medical therapy approved for CTEPH. Riociguat stimulates soluble guanylate cyclase and stabilises its association with NO, which in turn leads to vasodilatation. This drug finds its application in class I and IV PH.[73]

CHEST-1 was a double-blind, placebo-controlled trial in which inoperable CTEPH subjects or postoperative patients with persistent or recurrent PH were included (a total of 243 after drop-outs were excluded).[73] There was a significant improvement in 6MWD (mean 39 m) at 16 weeks, which was the primary endpoint. Among the secondary endpoints, PVR and levels of NT-proBNP showed significant reductions. An extension of this study was carried out as CHEST-2 with 237 subjects in which the results were replicated with increased 6MWD and improved FC in 47%.[74] Thus, the favourable effect of riociguat was established by these two trials.

The PATENT-1 trial results published in 2013 provided evidence for the role of Riociguat in PAH.[46] A total of 443 patients with PAH were randomised into three groups and were given either a placebo or 2.5 mg riociguat three-times a day or an individually adjusted dose with a maximum of 1.5 mg riociguat three-times a day. Those individuals already receiving treatment in the form of ERAs or oral or inhaled prostanoids were also included. The change in 6MWD at 12 weeks was the primary endpoint, which significantly increased in the 2.5 mg subgroup. Among the secondary outcomes, PVR, FC, time to clinical worsening and dyspnoea score also saw significant improvements. The long-term safety and efficacy of the drug was studied in the PATENT-2 trial, which showed the benefits persisted with prolonged use up to 1 year.[48] Hypotension, syncope and pulmonary haemorrhage were the serious adverse effects seen in a few subjects in these trials.[47,48]

Another drug that appears promising in the medical treatment of CTEPH is macitentan, which was shown to significantly reduce PVR at 16 weeks in the MERIT-1 trial.[75] The drug was well tolerated along with other agents, such as PDE-5 inhibitors and non-injectable prostanoids.[62]

Although drugs can slow down disease progression, patients continue to deteriorate and lung transplant is the last resort when the condition is refractory to medical management.[76] Therefore, these patients should be referred for transplantation early so that they may be listed once the disease course worsens.

Combination Therapy: the New Kid on the Block

Curbing multiple pathogenesis pathways simultaneously was researched; however, the initial BREATHE-2 trial failed to find any significant response to dual therapy of bosentan and epoprostenol.[60] Several RCTs did show favourable outcomes but it was the large-scale AMBITION trial on the use of ambrisentan and tadalafil for PAH that established the role of dual therapy.[77] The AMBITION trial involved 500 subjects with either iPAH or CTD-associated PAH who were either treatment naïve or had received treatment for <14 days. Patients were randomised into three groups, in

which 253 subjects received dual therapy with ambrisentan and tadalafil, 126 received monotherapy with ambrisentan, and the remaining 121 were kept only on tadalafil. The primary outcome was disease worsening or hospitalisation, which was significantly lower in the dual therapy group. The secondary outcome of satisfactory clinical response at 24 weeks was significantly higher in the combination therapy. The discontinuation rate because of side effects was almost the same across all three groups. This study established the superiority of dual therapy over monotherapy beyond any doubt.[77]

The long-term effect of upfront dual therapy was examined in ITALY study.[78] In this retrospective analysis, 56 patients with PAH on an upfront combination of ambrisentan plus tadalafil were followed up for 12 months. The use of upfront combination therapy resulted in significant improvement in WHO FC, NT-proBNP, exercise capacity, 6MWD and pulmonary haemodynamics.

Later, the OPTIMA trial explored a combination therapy of macitentan plus tadalafil in 50 treatment-naïve patients with PAH.[79] At 16 weeks, PVR had fallen significantly by 45% from 11.7 ± 4.7 WU to 6.5 ± 3.6 WU. Simultaneously, mPAP fell by 7.83 mmHg, cardiac index increased by 0.91 l/min/m^2, total pulmonary resistance decreased by 5.4 WU, mixed venous oxygen saturation increased by 5.5 %, 6MWD increased by 35.8 m and NT-proBNP was reduced by 68%. Peripheral oedema, headache and diarrhoea were the most prevalent adverse events but few patients had to discontinue therapy because of side-effects.

Another shot in the arm for upfront dual therapy comes from the recently announced positive result of the phase III A DUE trial at the annual scientific sessions of American College of Cardiology.[80] The study randomised 187 patients with PAH to a combination therapy of macitentan 10 mg plus tadalafil 40 mg versus monotherapy with either drug. Both treatment-naive patients and those on prior therapy were included and were followed up for 16 weeks. The primary endpoint was change in PVR from baseline. Mean participant age was 51 years and the median time of PAH duration was 2.5 years. The use of combination therapy led to significantly lower (almost double) PVR at 6 weeks compared to tadalafil monotherapy (−22 versus −44 %; p=0.0001) and for macitentan monotherapy (−23 versus −45%; p<0.0001). The secondary endpoint of 6MWD was also lower with combination therapy compared to monotherapy with either drug. No safety issues were seen with combination therapy.[80]

The Road Ahead: Triple Therapy

The rapidly progressive course of PH led to research and approval of upfront dual drug therapy and now there are efforts in the direction of triple therapy to prevent right heart failure.

The Phase III, double-blinded, placebo-controlled TRITON trial was undertaken with initial therapy with tadalafil, macitentan and selexipag versus tadalafil, macitentan and placebo. While there was no significant difference in terms of haemodynamic improvement between the two arms, an exploratory long-term analysis did suggest a better long-term outcome with the triple therapy.[81]

Another study, by Michele et al., found triple therapy with tadalafil, ambrisentan and treprostinil in subjects with idiopathic PH not only led to functional and haemodynamic improvement but also caused reversal of right heart remodelling. Although the small study size is a limitation, it has shown a long-desired result in terms of reverse remodelling.[82]

With Interstitial Lung Disease: More Therapeutic Options

For the treatment of pulmonary hypertension in patients with interstitial lung disease (ILD), there are presently no specific authorised treatments. A poor prognosis, worse quality of life and additional impairment in exercise tolerance are linked to PH, which can occur in 15–86% of individuals with ILD.[83]

Off-label use of vasodilators for PAH has been attempted with varying degrees of success and occasionally with negative consequences. The STEP-IPF trial with sildenafil, MUSIC trial with Macitentan and RISE-IIP trial with riociguat failed to demonstrate any benefit with these drugs.[84–86] A combination of nintedanib (an antifibrotic drug approved for ILD) and sildenafil failed to have any impact on PH in the INSTAGE study.[87] Similarly, the addition of pirfenidone (another antifibrotic drug approved for ILD) to sildenafil failed to improve outcomes in SP-IPF study.[88]

However, in 2021 the use of inhaled treprostinil produced a windfall in ILD-PH management with publication of landmark INCREASE trial.[89] The INCREASE study was a Phase III RCT (randomised, double-blind and placebo-controlled) that assessed the impact of the inhaled prostacyclin analogue treprostinil on exercise tolerance in PH-ILD patients. A total of 326 patients were randomly randomised to receive treprostinil via inhalation versus a placebo. The two groups' baseline characteristics were comparable. At 16 weeks, the use of treprostinil led to a significant 31.12 m increase in 6MWD from baseline. Concomitantly, there was a 15% fall in NT-proBNP levels with therapy, while clinical worsening also saw a 40% decline with inhaled treprostinil.

A long-term, open-label extension (INCREASE-OLE) study showed the drug's safety and efficacy until 52 weeks.[90] In the INCREASE-OLE study, all patients discontinued the treatment received during the RCT and received inhaled treprostinil at 0.6 mg/ml via an ultrasonic pulsed-delivery nebuliser at 6 µg per breath regardless of their assigned treatment arm in the RCT. The positive results led to the first regulatory approval by FDA of a drug specifically for ILD associated with PH.[91] The label indicates use in ILD-PH, including idiopathic interstitial pneumonia (IIP), combined pulmonary fibrosis and emphysema (CPFE) and CTD for improving the exercise capacity. Based on positive data from BREEZE study (see above), the treprostinil DPI form was approved for use.[70]

Ongoing studies on the dry powder form of inhaled treprostinil, such as DEciPHer-ILD (NCT06388421) in patients with ILD and PH, ASCENT (NCT06129240) in group 1 and group 3 PH and SAPPHIRE (NCT03814317) in patients with sarcoidosis-associated PH, are expected to further expand the scope of the drug in PH. Another study (NCT04691154) is using liposomal treprostinil inhalation suspension in ILD-PH.

Another molecule, inhaled nitric oxide (iNO), has shown success in ILD-PH in the iNO-PF study.[92] The study enrolled 23 patients with ILD-PH and randomised them to iNO (30 mg/kg) versus placebo for 8 weeks. There was improvement in moderate vigorous physical activity and clinical overall activity. An open label extension arm with higher doses of iNO administered for an additional 16 weeks found the therapy to be safe. More recently, a small study of 44 patients used pulsed iNO via a dedicated device (INOpulse; Mallinckrodt) in ILD patients and demonstrated improvement in moderate vigorous physical activity.[93] An ongoing study (NCT05867914) is using a novel 3P-100 device (Third Pole Inc.) for delivering iNO at doses of 2 6 mg/h and 6 mg/h for around 2 hours for each.

Treatment without Cardiopulmonary Comorbidities

Managing patients with PAH requires a multidisciplinary treatment strategy because it is an uncommon and potentially fatal condition. Achieving and maintaining a low-risk profile on optimised medical therapy is recommended as a treatment goal in patients with PAH. The comprehensive care of individuals with PAH also includes general interventions, including supplemental oxygen, diuretics to improve volume status, psychosocial support and structured exercise instruction. Treatment of IPAH, HPAH, DPAH or PAH-CTD should be based on risk stratification, the existence or absence of cardiopulmonary comorbidities and the severity of the disease.[18]

It is advised to begin combination therapy with ERA and PDE-5 inhibitors for patients without cardiovascular comorbidities at low or intermediate risk.[18] This strategy was evaluated in the AMBITION trial, which compared first combination therapy using ambrisentan at a dose of 10 mg orally twice daily and tadalafil at a dose of 40 mg orally twice daily, with initial monotherapy with either drug. In the TRITON study, PAH patients who had never received medication were given either an initial triple-combination therapy with selexipag up to 1,600 mg once daily, tadalafil doses up to 40 mg once a day, macitentan 10 mg or an initial dual-combination therapy with macitentan and tadalafil with a matching placebo. Most of the patients in Triton had iPAH, HPAH, DPAH, or PAH with CTD. Although TRITON did not show a benefit of initial oral triple combination therapy over initial double-combination therapy, it did demonstrate that initial double-combination therapy can significantly enhance haemodynamics and exercise capacity. Initial dual-combination therapy with ERA and PDE-5 inhibitors is advised for newly diagnosed individuals who present at low or intermediate risk. Further research is required to discover whether oral triple-combination medication affects long-term outcomes. Due to the paucity of available data, initial oral triple-combination therapy is not advised. In patients at high risk, initial triple-combination therapy, including an intravenous or subcutaneous prostacyclin analogue, should be considered.

Treatment with Cardiopulmonary Comorbidities

First-line monotherapy with a PDE-5 inhibitor or an ERA should be considered for patients with iPAH/HPAH/DPAH and cardiac comorbidities. Additional PAH drugs may be considered individually in patients with IPAH/HPAH/DPAH and cardiac comorbidities who present at intermediate or high risk of death while on PDE5-i or ERA monotherapy. For patients with PAH who are not responding to optimal medical therapy, lung transplantation is still a viable therapeutic option.[18]

Agents in the Pipeline

Ralinepag

Ralinepag is a next-generation prostaglandin receptor agonist that has shown promising results in a Phase II clinical trials in group 1 PH in terms of reducing PVR and tolerability of the drug over 22 weeks of treatment. Headache, nausea and diarrhoea were the most common adverse effects reported.[94]

ADVANCE OUTCOME (NCT03626688) and ADVANCE CAPACITY (NCT04084678) are ongoing Phase III trials with the aims of assessing, respectively: safety and efficacy; and effect on exercise capacity.

Sotatercept

One tumour growth factor-β (TGF-β) substance is BMPR-2, which plays a role in maintaining the integrity of the pulmonary endothelium and in the aetiology of hereditary PH. Mutations in the BMP pathway lead to excessive endothelial cell growth.[95]

Sotatercept is a novel molecule consisting of human immunoglobulin G bound to one of the activin receptor type II A domains as a single fusion protein. It performs as a decoy ligand for the TGF-β family of proteins, leading to downregulation of proliferative and anti-apoptotic forces in pulmonary vasculature. In effect, it works as an activin signalling inhibitor and restores the balance between cellular growth, promoting and inhibiting pathways.[95]

Its efficacy, tolerability and safety were proven in group 1 PH subjects with ongoing background therapy in the phase II PULSAR trial.[95] Two dosages of the drug (0.3 mg/kg and 0.7 mg/kg administered subcutaneously every 3 weeks) were tried in 107 patients for 24 weeks. Both dosages were shown to have favourable effects on pulmonary haemodynamics, 6MWD and NT-proBNP levels compared to placebo. Significant improvements in PVR were seen at the end of 24 weeks, more with the 0.7 mg/kg dose. Thrombocytopenia and am increase in haemoglobin were important side effects.[95] An open-label extension of the study revealed sustained benefits and safety up to 24 months.[96]

The SPECTRA and STELLAR trials also assessed the efficacy of sotatercept with encouraging results.[97,98]

The SPECTRA trial evaluated the impact of the drug on exercise parameters in invasive cardiopulmonary exercise testing. The primary endpoint was change in peak oxygen consumption (VO_2 max) after 24 weeks of therapy. The initial results from 10 patients revealed a rise in VO_2 max and total workload. At the same time, mPAP, pulmonary artery wedge pressure and mean right atrial (RA) pressures fell significantly.[97]

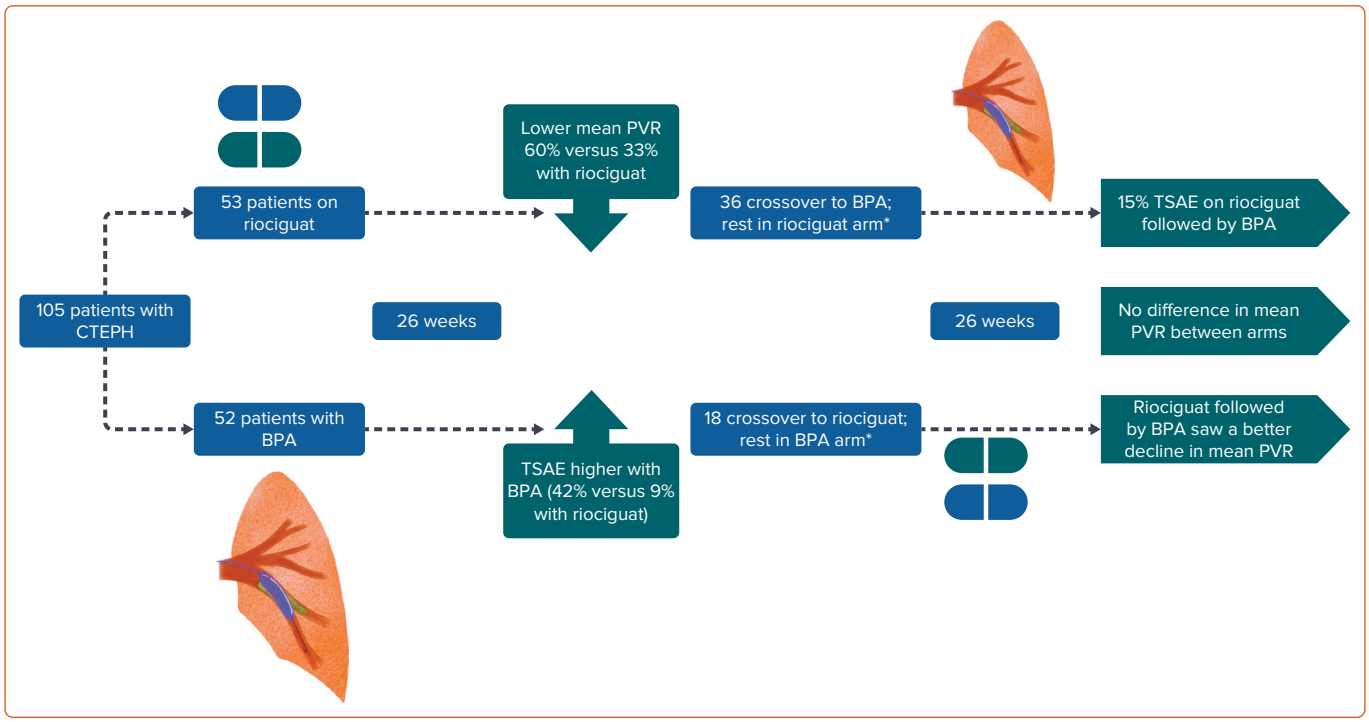
To date, STELLAR is the largest study of the drug, with 163 patients with PAH followed over 26 weeks. The results showed that, in patients with PAH who were receiving stable background therapy, sotatercept resulted in a greater improvement in 6MWD (+40 m than placebo. There were also improvements in secondary endpoint, such as PVR, NT-proBNP, WHO FC, time to death or first occurrence of a non-fatal clinical worsening event, French risk score, PAH-SYMPACT Score (physical impact and cardiopulmonary domains) and multicomponent improvement (all of 6MWD, NT-proBNP level and WHO FC). The time to death or first occurrence of or non-fatal clinical worsening event was significantly improved by sotatercept (HR 0.16); the benefits were apparent at 4 weeks and the curves continued to separate till 32 weeks. Epistaxis, telangiectasia and dizziness were the main adverse reactions. Haematological abnormalities, such as increased haemoglobin and low platelet count, were higher with sotatercept.

Based on the positive results from the STELLAR study, the FDA has approved sotatercept as a S/C injection every 3 weeks for group 1 PH in March 2024.[99] The drug should be initiated at a dose of 0.3 mg/kg while the target dose recommended is 0.7 mg/kg. Dosage can be modified based on haemoglobin and platelet level. The label is for improvement in functional class, exercise capacity and attenuation of clinical worsening. Ongoing studies, such as HYPERION (NCT04811092; intermediate- and high-risk PAH), MOONBEAM (NCT05587712; children), SOTERIA (NCT04796337; long-term study) and ZENITH (NCT04896008; WHO FC 3 or 4 with high mortality risk), will shed further light on the role of drug in other facets of PAH.

Mirivadelgat

Mirivadelgat is an activator of aldehyde dehydrogenase 2 activator (FP-045) being developed by Foresee Pharmaceuticals. In an ongoing phase

Figure 3: Balloon Pulmonary Angioplasty versus Riociguat for Pulmonary Hypertension: Summary of RACE Trial[115]



**No further BPA sessions were done. BPA = balloon pulmonary angioplasty; CTEPH = chronic thromboembolic pulmonary hypertension; PVR = pulmonary vascular resistance; TSAE = treatment associated serious adverse events.*

2 study WINDWARD (NCT06475781), patients with ILD-PH confirmed by RHC are being randomised to 150/300 mg of mirivadelgat versus placebo. The main outcome measure is change in 6MWD, time to clinical deterioration from the baseline (predefined and adjudicated clinical events), biomarker levels change (NT-proBNP and procollagens) and patient-reported outcome measures, all at 12 weeks.

Response Predictor: Super-responders

For a long time, it has been known that CCBs are effective only for group 1 PH patients who had a positive vasoreactivity test.[57,100] Numerous studies have been done to ascertain if there are certain factors which can predict the response to a group of drugs.[101]

In the STRIDE trial conducted by Benza et al., it was seen that in PH subjects receiving ERAs, those with the GNG2 variant of the G-protein receptor had a greater improvement in 6MWD.[102] In another study by Gabler et al., women taking ERAs were seen to have a greater rise in 6MWD compared to their male counterparts with a statistically significant difference.[103] As for PDE-5 inhibitors, male sex, younger age, lower baseline 6MWD and idiopathic or hereditary PH were associated with better response.[104]

Minimally Invasive Procedures

Long-standing PH results in elevated right ventricular pressure and eventually right heart failure, which leads to severe haemodynamic impairment. To alleviate the raised right heart pressure while waiting for a lung transplant, procedures, such as atrial septostomy, Potts shunting and its modifications, have been used.[105] In the AFR-PRERELIEVE trial, atrial flow regulator implantation improved haemodynamics and exercise capacity.[106] The drawback of all these procedures is the admixture of venous blood into the arterial circulation with subsequent reduced oxygen saturation.[105]

Pathogenic mechanisms include sympathetic overdrive and over-activation of the renin–angiotensin–aldosterone system secondary to low cardiac output leading to vasoconstriction and remodelling.[107,108] Different strategies have been aimed at these mechanisms, including sympathetic ganglion block, pulmonary artery denervation (PADN), and renal denervation.[109–113] Zhang et al. carried out a large, multicentre RCT with PADN in one arm and sildenafil in another in patients with combined pre- and post-capillary PH. The PADN group did significantly better in terms of PVR as well as 6MWD.[114] This method is gaining attention as it has the potential for reducing the requirement of lung transplant.

Balloon pulmonary angioplasty (BPA) is emerging as an established mode of treatment for CTEPH/CTEPD. The major indications would be patients who are inoperable and those with recurrence after surgical treatment.[18] The consensus is that distal segmental and subsegmental branches (vessel diameter of 0.5–10 mm) are best suited for BPA while proximal PA and proximal segmental vessels (size >2 mm) are easily managed by surgery. Very distal branches are best left on medical management. However, there is significant learning curve with BPA and long-term outcome data is lacking. Potential complications include vessel injury, lung injury, haemoptysis and hypoxia.

The recently published RACE trial randomised 105 patients with inoperable CTEPH with (PVR >320 dyne/s/cm^{-5}) to riociguat versus BPA.[115] In this multicentre study across 23 centres in France, the primary endpoint was change in PVR at 26 weeks. Following this, an open-label, cross-over study of 26 weeks was performed with BPA as an add-on to a riociguat group and vice versa (*Figure 3*). At 26 weeks, the reduction in PVR from baseline was around 60% in the BPA group and 33% in the drug arm ($p<0.001$). However, serious adverse events were higher in the BPA group (42% versus 9%); nonetheless, there were no deaths. At 52 weeks, the reduction in PVR was similar in both groups. In the Riociguat followed by

BPA group the complication rate was one-third lower (14% versus 42%), indicating that a strategy of drug therapy before BPA could be beneficial. Ejiri et al. demonstrated that vascular injury during BPA can be safely addressed in majority of cases by a graded strategy of heparin reversal, balloon occlusion and gelatin sponge embolisation.[116]

Surgical Options

The final therapeutic option for FC 3 and 4 patients not responding to medical management is lung transplant. Apart from minimally invasive techniques, implantation of right ventricular assist devices has been tried as a bridge therapy to transplants or in those in whom the transplant is contraindicated.[117]

An ongoing single-arm, multicentre trial ASPIRE PH (NCT04555161) is studying a novel device, the Aria CV PH system, in which a software-controlled pulsating balloon is inserted into the pulmonary artery.[118] The ARIA CV is an investigational device consisting of a reservoir, balloon, a connecting conduit and a holding anchor. The inflation occurs in right ventricular diastole and deflation in systole, assisting function. The results remain to be seen.

For CTEPH, surgical management is the preferred modality.[119] Pulmonary endarterectomy is the treatment of choice as it is curative and should be considered in all patients who are operable. It is imperative that the centre holds adequate expertise and experience for a better outcome of this procedure. BPA may be an option for those with contraindications to PEA, such as inaccessible obstruction, highly elevated mPAP or significant comorbidities.[18,33] Right ventricular pacing is another modality to improve the function of the right ventricle in CTEPH as well as other groups of PH.[105]

Changing Philosophy and Future Directions

PH is no longer an orphan disease with a short-term fatal outcome. Survival has improved from a mean 2.8 years to over 5 years.[41,119] The perspective has changed in terms of research as well. The three major trials – AMBITION, SERAPHIN and GRIPHON – differed from the previous studies in terms of enrolling large numbers of study subjects from multiple centres, having better-defined outcomes rather than mere reliance on 6MWD and allowance of background PH therapy.[120]

The recognition of borderline elevated pulmonary pressure as a risk factor for PH has resulted in a new haemodynamic definition and early diagnosis.[12,121] Efforts have been made to refine the risk stratification strategy.[39–43]

Upfront dual combination therapy has been established and triple therapy is successfully being explored with success.[122]

The approach has shifted towards earlier recognition and vigorous attempts to slow down or halt the progression. Even in non-responsive cases, attempts can be made to assist the right ventricle and reduce the requirement for lung transplant.[105]

Conclusion

The management of pulmonary hypertension is an ever-changing field. While it was once considered an orphan disease, novel diagnostic and therapeutic pathways have, without doubt, improved survival.

The ability to enhance goal-oriented treatment decisions is provided by the new diagnostic criteria and redefined risk stratification, and nuanced phenotyping should lead to further improvement in clinical outcomes. The FDA approval of inhaled treprostinil and sotatercept for the treatment of PH was a considerable milestone in the PH timeline.

Future medical advances, such as a potential fourth or fifth therapy pathway for PAH, hold considerable promise. Beyond prescription drugs, we now have a better understanding of the value of supervised exercise training in stable PH and the potential value of interventional therapy in some circumstances. Because of the dedication and global cooperation of patients, researchers, and medical professionals, the future is hopeful. ❑

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