CARDIOLOGY Rounds®

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# Evidence-based Management of Pulmonary Hypertension

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**Pulmonary-arterial hypertension (PAH) from any cause is more prevalent than previously believed, and significant uncertainties remain regarding the diagnosis and optimal treatment of PAH. It is now recognized that effective treatment for one cause of PAH may not necessarily be useful for PAH from a different cause. This issue of *Cardiology Rounds* reviews the contemporary definition, classification, and diagnosis of PAH, with a focus on recent developments in its treatment.**

## Definition, epidemiology, and natural history

PAH is a devastating disease, characterized by progressive increases in pulmonary-vascular resistance (PVR) and pulmonary-artery pressure (PAP).[1] Initially described by Dresdale et al,[2] PAH is defined as the presence of a resting systolic PAP ≥30 mm Hg or a mean PAP ≥25 mm Hg (Table 1). PAH was thought to be a relatively rare disease, with a global incidence of 1-2 cases/million;[1] however, more recent data from the Centers for Disease Control suggest that PAH from any cause is more prevalent than previously thought.[3] Predominantly affecting women (female:male ratio 2:1), the incidence of PAH appears to follow a bimodal distribution, affecting young women of reproductive age, as well as women in their fifth and sixth decades of life. Median survival after diagnosis is 2.8 years without treatment.[4]

## Classification

In 2003, the World Health Organization (WHO) classified pulmonary hypertension (PH) into 5 broad categories according to etiology: PAH, PH secondary to left-heart disease, PH secondary to lung disease, PH secondary to chronic thromboembolic disease, and miscellaneous conditions. PAH is further subdivided into idiopathic (IPAH), associated PAH (APAH; eg, those connected with portal hypertension, scleroderma, or human immunodeficiency virus [HIV]), familial (FPAH), persistent PH of the newborn (PPHN), and PAH secondary to veno-occlusive disease (PVOD).[5] This method of classification is particularly useful because it highlights the different etiologies for PAH that, in turn, can better direct therapy. Furthermore, it provides prognostic information; for example, the prognosis for patients with APAH varies from PAH associated with HIV and scleroderma having a significantly reduced survival, whereas PAH secondary to congenital shunting is better.[6]

## Pathophysiology

The pathogenesis of PAH remains poorly understood and, since a number of conditions are associated with PAH, it is likely that the pathophysiology is multifactorial. A number of different pathways possibly related to the pathophysiology have been investigated,[7] such as: bone morphogenic protein type II receptor (BMPR II) mutations found in 50% of FPAH;[8,9] serotonin dysregulation (possibly linking appetite-suppressant drugs and PAH); smooth-muscle cell (SMC) voltage-gated potassium (K)+ channel dysfunction; serine elastase/matrix metalloproteinase (MMP) overactivity causing unchecked SMC proliferation; and endothelial-cell (EC) apoptosis causing selection of an apoptosis-resistant population, and paradoxically leading to proliferation and pulmonary-arteriolar occlusion.[10,11]

Despite a multitude of inciting factors, the final common pathway in PAH is the elevation of PVR. Through the synthesis and release of vasoactive factors, the EC lining of the pulmonary vasculature plays a critical role in maintaining the delicate balance between vasoconstriction (thromboxane A2, endothelin-1) and vasodilation (prostaglandin $I_2$, nitric oxide [NO]). Thus, EC damage and/or dysfunction upset this homeostasis, tilting the balance in favour of vasoconstriction.

## Symptoms and signs

The onset of PAH is often insidious, with symptoms only presenting once the disease is well established. The cardinal symptom of PAH is dyspnea, primarily due to pulmonary vasoconstriction leading to hypoxemia. Other symptoms are reflective of right-ventricular (RV) failure, including fatigue, syncope,

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**Table 1: Hemodynamic definitions of PAH**

| | |
|---|---|
| **Systolic PAP** | ≥30 mm Hg (rest)<br>≥35 mm Hg (exercise) |
| **Mean PAP** | ≥25 mm Hg (rest)<br>≥30 mm Hg (exercise) |
| **PCWP** | ≤15 mm Hg |
| **PVR** | ≥3 Woods units (after ruling out increased pulmonary flow as a cause of elevated pressure) |

PAH = pulmonary-artery hypertension; PAP = pulmonary-artery pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary-vascular resistance

peripheral edema, and abdominal distension. Additional clinical presentations, such as Raynaud phenomenon (eg, CREST syndrome, a connective tissue disease comprising calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia), signs of chronic liver disease (porto-pulmonary hypertension), or opportunistic infections (HIV-associated PAH), may also be encountered depending on the associated cause of PAH.

## Assessment of PAH

PAH is a diagnosis of exclusion; therefore, patients presenting with PH must first be assessed for the various causes. A directed history and physical examination to determine causes and severity of PH is important, along with routine blood work, a baseline electrocardiogram (ECG), chest x-rays (CXRs), and an echocardiogram. Computed-tomographic (CT) scans of the chest, pulmonary-function testing (PFT), and a ventilation/perfusion scan can help assess for lung disease or pulmonary emboli. In addition, sleep studies are useful for considering a diagnosis of sleep apnea and echocardiograms can assess for left-ventricular (LV) dysfunction/valvular abnormalities and shunting, as well as quantify the degree of PH. Although Doppler echocardiography has become a popular screening tool in the diagnosis of PH, and some clinical trials use it as the only measure of PH severity in response to treatment, data suggest that it is relatively imprecise.[12] Nevertheless, there is a statistically significant relationship between RV systolic pressure determined by Doppler and catheterization,[13] yet, when subjected to precision analysis, these measurements are often inaccurate by as much as 38 mm Hg.[14] As a result, Doppler should not be used to decide when to treat patients on the basis of the magnitude of the PAP, and should not be used as the sole measure of efficacy to monitor therapy.

Autoimmune screening (connective tissue disease-associated PAH), HIV serology, and liver imaging (portal hypertension-associated PAH) are all important to examine for causes of APAH. If there is a familial history, genetic testing for BMPR II mutation may be indicated. Should the workup be negative, a diagnosis of IPAH is then made.

Right-heart catheterization is the gold standard for diagnosis. Vasodilator testing, most commonly using NO (10-80 parts/min), identifies patients who may respond favourably to calcium-channel blockade (CCB) therapy. A decrease of 10 mm Hg in mean PAP to <40 mm Hg constitutes a positive response. Pulmonary hemodynamics can also provide prognostic information.

## Treatment

Successful therapy for PAH would improve the quality of life as well as the life expectancy of the patient. For patients

**Table 2: World Health Organization (WHO) functional classification of PAH[15]**

| Class | Description |
|---|---|
| I | Patients with PH in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope. |
| II | Patients with PH who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope. |
| III | Patients with PH who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope. |
| IV | Patients with PH who are unable to perform any physical activity and who may have signs of right-ventricular failure. Dyspnea and/or fatigue may be present at rest, and symptoms are increased by almost any physical activity. |

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with secondary causes of PH, treatment should be directed at the underlying cause, eg, anticoagulation for thromboembolic disease, and angiotensin-converting enzyme (ACE) inhibitors/β-blockers for LV dysfunction. Patients with PAH should be classified based on WHO functional status (Table 2)[15] as well as risk stratification (Table 3) in order to define optimal treatment.

General supportive measures include salt restriction, diuretics, and oxygen supplementation, as needed. Anticoagulation with warfarin is usually reserved for patients with IPAH and chronic thromboembolic-major vessel PH (CTEPH). Few data exist[1] concerning the efficacy of warfarin in these circumstances; the target internationl normalized ratio (INR) ranges between 1.5-3.0 and is largely based on expert opinion. Initiation of vasodilator therapy was usually restricted only to those with WHO III or IV symptoms;[16,17] however, based on emerging data, recommendations state that therapeutic decisions should be based on a more thorough risk-stratification process (Table 3) rather than on functional class alone.[6] At present, lung transplantation is the only curative treatment for PAH. Atrial septostomy, which allows for unloading of the RV, can be used as a palliative measure or as a bridge to transplantation.

Drugs that promote vasodilation in the pulmonary circulation remain the mainstay for medical management with PAH. Options currently include prostacyclin and its derivatives, cyclic guanosine monophosphate (cGMP)-binding cGMP-specific phosphodiesterase (PDE-5) inhibitors, endothelin receptor (ETR) antagonists, and CCBs. In the algorithm from the American College of Chest Physicians in 2007,[16] intravenous (IV) epoprostenol is the first-line therapy for patients with severe disease. Oral sildenafil (PDE-5 inhibitor) and bosentan (ETR antagonist) are recommended for patients with advanced PAH; combination therapy is an option for patients not responding to the initial therapy. Individual classes of drugs used in PAH are considered below.

### *Calcium-channel blockers*

CCBs are indicated in patients who have a positive response to vasodilator testing (≥10 mm Hg decline in mean PAP [mPAP] and mPAP ≤40 mm Hg). Sitbon and colleagues[18] reported results of a retrospective analysis of 557 IPAH patients tested acutely with IV epoprostenol or inhaled NO,

**Table 3: Risk stratification of patients with PH**

| Lower | Determinants of risk | Higher |
|---|---|---|
| No | **Clinical evidence of RV failure** | Yes |
| Gradual | **Progression** | Rapid |
| II, III | **WHO class** | IV |
| Longer (>400 m) | **6-minute walk distance** | Shorter (<300 m) |
| Minimally elevated | **BNP** | Very elevated |
| Minimal RV dysfunction | **Echocardiographic findings** | Pericardial effusion Signif. RV dysfunction |
| Normal/near normal RAP and CI | **Hemodynamics** | High RAP, low CI |

BNP = B-type natriuretic peptide; RV = right-ventricular; RAP = right-atrial pressure; CI = cardiac index

and examined the long-term efficacy of CCBs. Long-term responders were defined as patients in New York Heart Association (NYHA) functional class I or II with a sustained hemodynamic improvement after at least 1 year without the addition of other PAH-specific therapy. Of 70 patients who had positive vasodilation responses, 38 had improvement at 1 year ("long-term responders"). When compared with patients who had a positive vasodilator test, but did not show improvement at 1 year, long-term responders had better NYHA class and hemodynamics at baseline, and greater reductions in mPAP and PVR with vasodilator testing.

Patients with IPAH who meet the above criteria may be treated with CCBs. True responders to vasodilators (CCBs) are very uncommon among patients with other forms of PAH (non-IPAH, or PAH occurring in association with underlying disease processes), and long-acting nifedipine or diltiazem, or amlodipine are suggested. Due to its potential negative inotropic effects, verapamil should be avoided. Patients should be closely followed for both safety and efficacy, with an initial reassessment after 3 months of therapy.[18]

## *Prostanoids*

Prostacyclin ($PGI_2$) is a membrane-derived signalling molecule whose production is catalyzed by prostacylin synthase in endothelial cells.[2] It has a number of effects on the pulmonary vasculature, including inhibition of SMC constriction and proliferation, as well as platelet aggregation.[6] Epoprostenol, the IV formulation of prostacyclin, remains the gold-standard treatment for PH and demonstrates improved morbidity and mortality. Common side effects include flushing, nausea, diarrhea, and joint pain.

In 1996, Barst et al[19] published results of the first randomized, prospective major trial of IV prostacylin; this trial recruited 41 patients with NYHA class III or IV and compared IV epoprostenol plus conventional treatment (diuretics and anticoagulation) with conventional treatment alone. Prostacyclin treatment revealed significant improvements in symptoms, 6-minute walk distance (6MWD), hemodynamics (mean PAP and PVR), and survival at 12 weeks.

Although effective, there are notable drawbacks to prostacyclin therapy: the total cost can be in excess of $100,000 per year; morbidity is associated with continuous IV infusion; and the drug requires refrigeration, since it becomes unstable at room temperature. More recently, a number of prostacyclin analogues have been developed to address these concerns;[16,20] these include oral (beraprost), inhaled (iloprost), and subcutaneous prostacyclin (treprostinil). Compared with placebo, these agents have demonstrated some significant improvements in morbidity, but not in mortality; however, they have not been directly compared with prostacyclin.

## *Phosphodiesterase inhibitors*

NO is a powerful vasodilator that acts via cGMP, and the activity of cGMP is limited by phosphodiesterase-5 (PDE-5), an enzyme that inactivates cGMP through conversion to 5′ GMP. Sildenafil, an oral PDE-5 inhibitor, is therefore able to potentiate NO and promote vasodilation of pulmonary vasculature.[21] NO has also been demonstrated to attenuate SMC proliferation.[22] Sildenafil is a potent and highly specific PDE-5 inhibitor that has been previously approved for erectile dysfunction. Several reports[16,23] of nonrandomized, single-centre studies in PAH patients treated with long-term sildenafil suggested its promise as a therapeutic agent. Sildenafil is administered orally (20 mg, 3 times/day) for the treatment of PH. It has a relatively favourable side-effect profile; the most common side effects are headache (16%) and skin flushing (4%-8%).[24]

The Sildenafil Use in Pulmonary Arterial Hypertension-1 (SUPER) study[25] was a randomized, double-blind trial that compared placebo and incremental doses (20 mg, 40 mg, and 80 mg) of sildenafil in 278 symptomatic PAH patients (majority WHO class III-IV). At 12 weeks, patients receiving sildenafil had significantly improved 6MWD, mean PAP, and WHO functional class. The incidence of clinical worsening did not differ significantly between the patients treated with sildenafil and those treated with placebo. This trial was not powered to detect mortality differences.

## *Endothelin-receptor antagonists*

Endothelin-1 is a potent vasoconstrictor and mitogen[26] that exerts its effects by binding to endothelin A and B receptors.[27] Activation of endothelin B receptors has also been found to have counterregulatory effects, through activation of NO and $PGI_2$.[6,28] The ETR antagonists have been studied in numerous open and several controlled clinical trials in patients with PAH.[29] The differences between the Food and Drug Administration (FDA)-approved drugs may be due to ETR selectivity, but it may also be linked to other properties, such as pharmacokinetics or drug-drug interactions.

***Bosentan:*** Bosentan is an orally active (twice-daily dosing), nonpeptidic, nonselective, sulphonamide-class ETRA/ETRB antagonist. It was the first ETRA to receive approval for the treatment of patients with PAH of NYHA functional class III (Europe, US, and Canada), and NYHA IV (US and Canada), at a target dose of 125 mg twice daily. In 2 randomized, controlled trials, bosentan improved exercise capacity, functional class, hemodynamics, and time to clinical worsening.[30,31] Additional open-label, long-term studies in patients with PAH demonstrated persistent efficacy of bosentan over time and the potential for improved survival, compared with predicted survival.[32,33] Since these initial pivotal studies, significant benefits of bosentan treatment have been demonstrated in separate studies under the Bosentan Randomized Trials of Endothelin Antagonist Therapy (BREATHE) program in children with PAH (BREATHE-3: idiopathic PAH and congenital heart disease),[34] in PAH associated with HIV (BREATHE-4), in patients with PAH and Eisenmenger syndrome (BREATHE-5),[35] and in patients with portopulmonary hypertension.[36]

The Endothelin Antagonist tRial in miLdlY symptomatic PAH patients (EARLY) was the first study specifically designed to evaluate the effects of ETRA antagonism in 185 PAH patients in functional class II. The results are only available in abstract form,[37] preliminary results from this 6-month trial highlight a significant reduction in PVR, while the other primary endpoint, the 6MWD, did not reach statistical significance. The secondary endpoint, time to clinical worsening, improved with bosentan, translating into a 70% risk reduction. In another group of 157 patients with CTEPH (WHO Group IV), bosentan therapy led to significant reductions in PVR and improved dyspnea scores, while the 6MWD remained unchanged over the 6-month study period (BosEntan in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension [BENEFIT]).[38]

***Sitaxentan:*** Sitaxentan sodium is a selective ETRA antagonist of a sulphonamide class that has received approval for the treatment of PAH patients with WHO functional class III symptoms at an oral dose of 100 mg once daily (European Union, Canada, and Australia). To date, the FDA in the US has not approved sitaxentan, and a placebo-controlled study is currently planned (STRIDE-5) to provide additional data. The safety and efficacy of sitaxentan in patients with PAH has been clinically tested in the Sitaxentan To Relieve ImpaireD Exercise (STRIDE) program,[39] including 3 randomized, placebo-controlled trials (STRIDE-1,[40] STRIDE-2,[41] and STRIDE-4), 2 non-controlled studies (Study 211 and STRIDE-6),[42] as well as 3 long-term studies (STRIDE-1X, STRIDE-2X, and STRIDE-3). Sitaxentan significantly improved functional class (STRIDE-1, STRIDE-2, and STRIDE-4), 6MWD (STRIDE-1 and STRIDE-2), dyspnea score (STRIDE-1) and hemodynamics (Study 211 and STRIDE-1). Prolongation in the time to clinical worsening could only be demonstrated in a *post hoc* meta-analysis using pooled data from the 3 pivotal studies.[39] Long-term data are available from a small group of patients, suggesting that efficacy and safety are maintained for up to 12 months,[43] as well as preliminary data from the extension studies, with mean exposures of 26 (STRIDE-1X)[39] and 36 weeks (STRIDE-2X).[44] Data from subgroup analyses did not exhibit a clinically relevant treatment effect in patients with PAH associated with congenital heart disease.[39] In contrast, the subgroup of patients with PAH associated with connective tissue disease showed an increased 6MWD with sitaxentan treatment.[45]

***Ambrisentan:*** Ambrisentan is an orally active selective ETRA antagonist that belongs to the propanoic acid class.[46,47] In the US, ambrisentan has been approved at a dose of 5-10 mg once daily for PAH patients with WHO functional class II or III symptoms to improve exercise capacity and delay clinical worsening.[48] In Europe, ambrisentan was approved in April 2008 following a favourable opinion from the European Committee for Human Medicinal Products for the treatment of PAH patients in functional class II and III.[49,50] Results were from a 12-week, blinded-to-dose (1, 2.5, 5, or 10 mg daily) Phase II study[51] (improvements in 6MWD, functional class [FC], Borg score, quality of life, and pulmonary hemodynamics), and 2 pivotal studies, the AmbRIESentan in patients with moderate to severe PAH (ARIES-1[52] and ARIES-2[53]) that have not yet been published in full. The long-term follow-up of patients treated with ambrisentan in the 2 pivotal studies and the open-label extension (ARIES-E, n = 383) reveals that 95% were alive at 1 year and 94% were still receiving ambrisentan monotherapy, with sustained efficacy for improvement in 6MWD, dyspnea score and functional class.[54]

## Specific considerations

### *When and how to initiate therapy?*

The decision to start therapy and determine what agents should be used is best based on an assessment of the patient's risk. McLaughlin et al[6] proposed that risk stratification for patients take into account several variables, including RV failure, progression of symptoms, WHO class, 6MWD, B-type natriuretic peptide (BNP), echocardiographic findings, and hemodynamics. IV prostacyclin should be considered first-line for patients at highest risk; however, patients at lower risk with positive vasoreactivity should be initially managed with CCBs. Current opinions[1,6,16] favour either sildenafil or bosentan as acceptable first-line options, but management of patients who fit neither of these criteria remains more controversial. The EARLY trial[37] noted above was conducted in patients who were mildly symptomatic (FC class II) with relatively good functional capacity (6MWD = 431–438 m), and demonstrated that by 6 months, bosentan-treated patients had significantly lower increases in PVR compared with placebo and a better WHO FC. These data suggest that there may be a role for earlier treatment of PAH.

### *How do we stratify risk and monitor therapy?*

Once initiating therapy, patient responses must be assessed; proposed prognostic parameters are summarized below. These endpoints may be used to determine whether a patient is or is not achieving adequate therapeutic effects.

***FC:*** The WHO functional classification is a useful tool to evaluate the severity of PAH. The initial prostacyclin trials clearly demonstrated that FC correlates well with prognosis. For example, patients who initially present with FC III symptoms and are treated with epoprostenol have better survival at 5 years than those with FC IV symptoms (70% vs 27%).[4,6]

***6MWD:*** 6MWD is a relatively easy test to administer and has demonstrated a correlation with mortality in patients with PAH. One study in 43 PAH patients on differing treatment regimens and with different FC classes were divided into 2 groups based on their 6MWD.[55] The longer-distance group (>332 m) had significantly improved survival compared with those in the short-distance group. Among a number of other variables, including age, heart rate, norepinephrine level, and LV deformity index, only 6MWD independently correlated with mortality by multivariate analysis.

***Pulmonary hemodynamics:*** Although invasive, pulmonary hemodynamics can provide a significant amount of information both with regard to diagnosis and prognosis. In addition, measurement of the pulmonary capillary

wedge pressure is paramount in a patient with PH, because it has critical implications. In the Patient Registry for the Characterization of Primary Pulmonary Hypertension,[4] elevated mean right-atrial pressure, elevated mean PAP, and decreased cardiac index were associated with poor survival.

***BNP and other biomarkers:*** Among the biomarkers that have been studied, including BNP, atrial natriuretic peptide, and catecholamines, only BNP has been shown to predict mortality. In one study on patients with CETPH, those with BNP levels >150 pg/mL were found to have higher mortality.[56] At this time, since relatively few studies have been conducted, the use of BNP for prognostication in PAH has only received a grade C recommendation.[6] Although it is recognized that these measurements provide important information, they must be used in context, and their limitations appreciated. They fail to capture the full impact of treatment in patients with PH and should not preclude the collection of definitive data indicating the effect of therapy on the expression and time course of the disease.

### *Combination therapy*

Current PAH therapies target the different pathways (NO, endothelin-1, and prostacyclin) believed to play integral roles in pulmonary vasoconstriction, the hallmark of PAH. The potential for synergistic effects makes combination therapy an attractive option. The majority of evidence thus far is limited to open-label case series, although there are now 3 major randomized controlled trials that have examined combination therapy for PAH: BREATHE-2, the Safety and pilot efficacy Trial in combination with bosentan for Evaluation in Pulmonary arterial hypertension (STEP 1) and the sildenafil Add-on to Stable Epoprostenol Therapy study (PACES) .

***BREATHE-2:*** This randomized, double-blind, placebo-controlled trial compared epoprostenol +/- bosentan in 33 class III and IV patients.[57] By week 16, no significant differences in primary (>30% fall in total pulmonary resistance [TPR]) or secondary endpoints were seen. Leg edema was the only adverse effect observed more commonly in the combination-therapy group. One of the possible reasons for this essentially negative trial was a larger number of scleroderma-associated PAH patients in the combination-therapy group compared with epoprostenol-only treatment (18% vs 9%). Finally, this appeared to be a fairly ill population and the results of this trial may only suggest that in patients who are already maximally treated on epoprostenol, there is no further benefit with additional therapy. Therefore, the results would not be applicable to less ill patients who are not responding to monotherapy. Additional information is needed to evaluate the risk/benefit ratio of combined bosentan-epoprostenol therapy in PAH.

***STEP 1:*** STEP-1 was a randomized, double-blind, 3 month trial with a 1-year open-label extension;[58] 67 clinically stable patients already on bosentan for at least 4 months were randomized to receive add-on therapy: either inhaled iloprost (n=34) or placebo (n=33). Primary endpoints were 6MWD, NYHA class, Borg score, hemodynamic parameters by right-heart catheterization, and time to clinical worsening. Significant improvements in NYHA class, PVR, mPAP, and time to clinical worsening were seen in the combination therapy group vs placebo. There was a trend to improved 6MWD in the combination therapy group ($P$=0.051); thus the addition of iloprost significantly improves a number of clinical endpoints. However, one limitation for this study, as noted by its authors, is that STEP-1 does not clarify whether the observed improvements were due to iloprost alone, or to the additive/ synergistic effect of bosentan and iloprost. This could have been answered had there been a third group where iloprost replaced bosentan therapy, but this was not possible.

***PACES:*** The results of PACES have only been published in abstract form.[59] This 16-week (n = 267) double-blind, placebo-controlled randomized trial compared epoprostenol vs epoprostenol + sildenafil, with 6MWD as the primary endpoint. Secondary endpoints included hemodynamic parameters and time to clinical worsening. An improvement of 40 m was found in the 6MWD vs monotherapy ($P$=0.00088) and there were also significant improvements in all secondary endpoints reported, except for mean systolic blood pressure ($P$=0.07).

The ongoing trials of combination therapy in PAH are:

- **TRIUMPH**: stable dose bosentan or sildenafil +/- treprostinil; target enrollment = 267
- **COMPASS**: sildenafil +/- bosentan or bosentan +/- sildenafil
- **PHIRST**: naïve or bosentan +/- tadalafil; n=406
- VISION: sildenafil +/- iloprost (inhaled); target enrollment = 180
- **FREEDOM-C**: bosentan and/or sildenafil +/- treprostinil (oral); n= 300.

## Conclusions

As the understanding of PAH continues to evolve, so too do the therapeutic options available for this devastating disease. Developing an evidence-based approach to treating PAH will remain a constant challenge, mainly due to the rarity of PAH and thus the small number of patients enrolled in trials. Currently, the evidence indicates that manipulation of the NO, endothelin, and prostacyclin pathways is a viable therapeutic approach; however, a number of important questions remain about the best use of the drugs that have been developed. For example, the results of the EARLY trial call into question the usual practice of waiting until patients are FC III or IV before starting therapy. Combination therapy remains another murky area. Is combination therapy truly superior to monotherapy? Which agents are best used in combination? How does combination therapy affect the side effect profiles of these drugs? Cost is also a concern, since all of the currently available drugs are expensive when used as monotherapy alone. These issues all underline the need for additional well-designed and robust trials before widespread adoption of combination therapy for PAH is considered.

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