Combination Therapy in Pulmonary Arterial Hypertension: Is This the New Standard of Care?

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Abstract

Pulmonary arterial hypertension (PAH) is a rare, progressive, and potentially fatal cardiopulmonary syndrome that imposes a significant burden on patients in terms of morbidity and mortality, and on managed care organizations in terms of resource utilization. The majority of PAH-approved therapies are high-touch, high-management, high-cost treatments dispensed through specialty pharmacies. Current treatment guidelines recommend combination therapy for patients who show inadequate clinical response or who deteriorate on monotherapy. Combination therapies target 2, or sometimes 3, distinct PAH-associated signaling pathways: the endothelin, prostacyclin, and nitric oxide pathways. Registry data suggest that combination therapy is utilized in more than half of patients with PAH in the United States. Evidence supporting the use of combination therapy is provided through clinical trials, retrospective research, registry data, and expert guidelines. Managed care decision makers are charged with making population-based decisions on resource allocation. These decision makers must always consider cost, but must also be aware that clinical evidence suggests that early treatment with combination therapy can significantly reduce disease burden, may reduce hospitalizations, and should be considered when making coverage decisions.

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For author information and disclosures, see end of text.

Introduction

Pulmonary arterial hypertension (PAH), a subset of pulmonary hypertension conditions, is a rare but potentially fatal cardiopulmonary syndrome characterized by an abnormally high resting mean pulmonary arterial pressure (greater than or equal to 25 mm Hg), increased pulmonary vascular resistance (PVR) (greater than 3 Woods units), and a pulmonary arterial wedge pressure less than or equal to 15 mm Hg. Derangements in the 3 key biologic pathways (endothelin [ET], nitric oxide [NO], and prostacyclin [PGI_2]) in the pulmonary arterioles result in remodeling of the pulmonary vasculature, with progressive right heart dysfunction and, ultimately, right heart failure and death.[1-7] The annual incidence and prevalence of PAH in the United States has been reported as 2.3 and 12.4 cases per million, respectively.[8] The 1-year incident mortality rate is 15%.[6,9] Recent estimates from REVEAL (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) indicate that patients receiving PAH-specific treatment have a median survival of more than 7 years after diagnosis.[6]

The use of combination therapy was confirmed by the REVEAL data, which disclosed that at the time of enrollment, 46% of patients were taking 2 medications for PAH, and nearly 9% were taking 3 medications for PAH.[3,10-12] Additionally, 13 randomized controlled trials (RCTs)—almost half (43%) of major PAH trials—include a group of patients receiving combination therapy with 1 or more approved PAH drugs.[3] This is in part due to the ethical implications of conducting placebo-controlled studies with patients deprived of active treatment already proved to deter PAH progression. Recent trials have proved the safety and efficacy of combination therapies, including risk reduction in morbidity and mortality and decreased hospitalization.

Although there is no cure for PAH, there are 12 approved drug therapies to treat the disease. Most of

these therapies are dispensed through specialty pharmacies and are high-touch drugs with associated higher costs. Altogether, drug prescriptions dispensed through the specialty channel from 2013 to 2014 increased 5.8%, accounting for a 30.9% increase in spend for specialty medications. These drugs also account for a growing share (31.8% in 2014, up from 27.7% in 2013) of total overall drug spend and are expected to continue along this trajectory. The increases estimated by this trend calculation are likely modest, as roughly half of specialty medication drug costs are billed through the medical benefit and therefore are not included.[13] The increased use of combination therapy and the increasing specialty drug spend present a challenge for managed care decision makers as they face the task of making decisions to allocate resources for the maximum benefit of their members. This article will provide these decision makers with information and evolving clinical evidence affirming the potential for combination PAH therapy to become the standard of care.

Treatment Pathways in PAH

Currently, 3 pathways are implicated, with others being studied, in the pathologic mechanisms that lead to pulmonary vasoconstriction, inflammation, fibrosis, thrombus in situ, and vasculature remodeling in patients with PAH (**Figure 1**).[14,15] These pathways include the ET, PGI_2, and NO pathways and are targets for the current drug therapies. Approved PAH therapies include ET receptor antagonists (ERAs), prostacyclin analogues, phosphodiesterase-5 (PDE5) inhibitors, and a soluble guanylate cyclase (sGC) stimulator.[3,7,14,16]

ET-1 is a potent vasoconstrictor that induces vasoconstriction, smooth muscle cell proliferation, and fibrosis.[17] ET-1 acts via 2 receptors, ET_A and ET_B. In patients with PAH, elevated levels of ET-1 are commonly seen in the circulation and in the lungs, making it a natural target for pharmacologic blockade (**Table 1**).[7,18-29]

In patients with PAH, there is often decreased expression of prostacyclin synthase with reduced prostacyclin production in pulmonary artery endothelial cells, which leads to lower cyclic adenosine monophosphate levels, more vasoconstriction, and proliferation of underlying smooth muscle cells.[14] Prostacyclin analogues (Table 1)[18-29] promote vasodilation of the pulmonary and systemic arterial vascular beds, inhibit proliferation of smooth muscle cells, and inhibit platelet aggregation.[20,23,24,27-29] Supplementation of endogenous prostacyclin production with exogenous prostacyclin analogues has been shown to be an effective treatment for PAH.[7,23,24,27,29]

Patients with PAH also have low levels of circulating endogenous NO, which may contribute to some of the pathophysiologic processes of the disease. For instance, in the healthy lung, NO stimulates production of cyclic guanosine monophosphate (cGMP), which promotes vasodilation, and may also help inhibit smooth muscle cell proliferation. Low levels of NO may have the opposite effects in patients with PAH.[7,30-32] Expression of PDE5, which rapidly degrades cGMP, has been shown to be upregulated in patients with PAH.[7,31] By blocking PDE5, selective PDE5 inhibitors (Table 1)[7,18-29] prevent the degradation of cGMP.[18,25,31] Lastly, augmentation of sGC activity with an sGC stimulator is an alternative option for targeting the NO pathway since the sGC activator is not limited by low endogenous NO levels.[19,33]

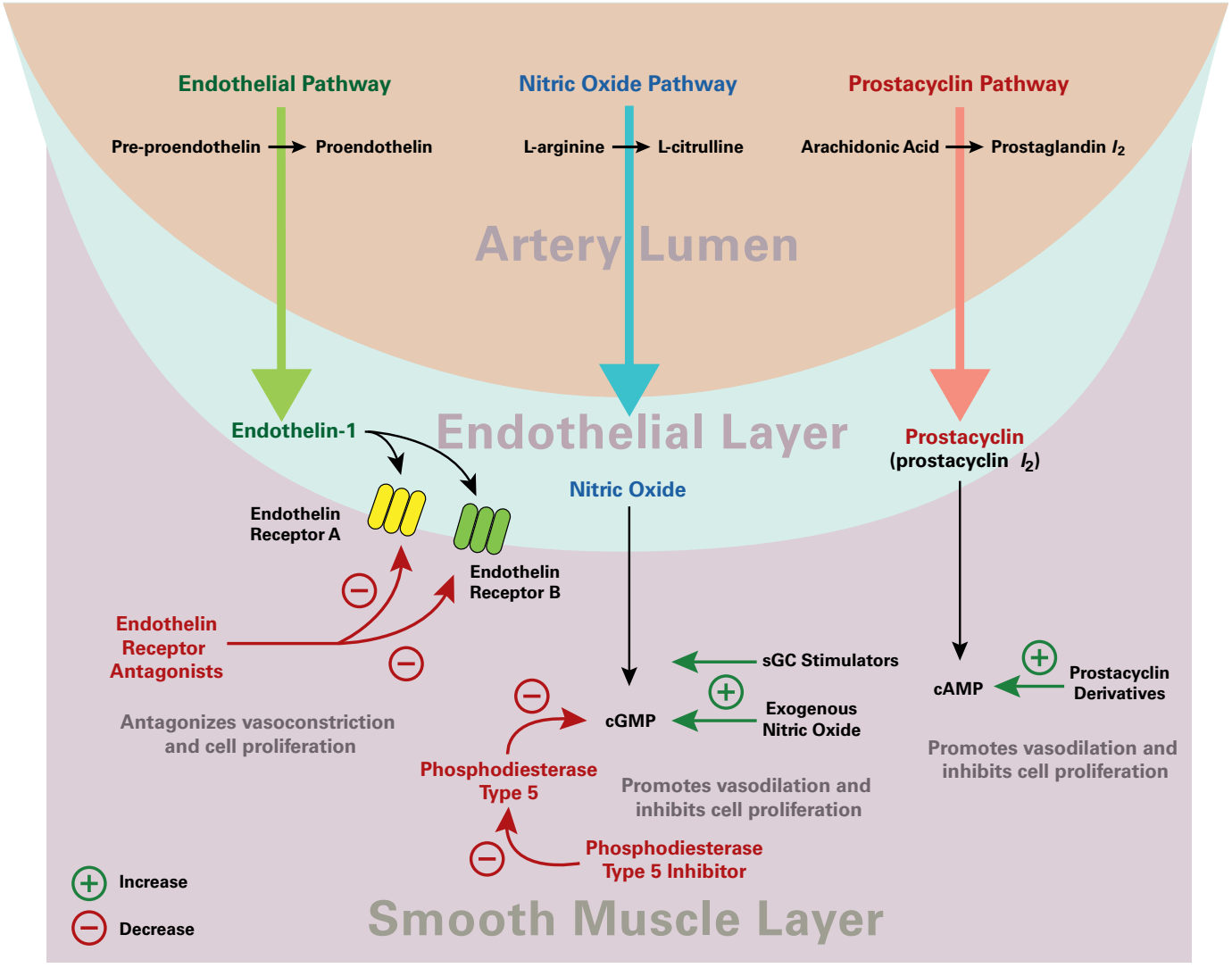
Combination therapy, using distinct and complementary mechanisms of action, targets the derangement in multiple key biologic pathways in the pulmonary arterioles to improve PAH symptoms. Thus, combination therapy is a valuable option for management of patients with PAH (Table 1).[7,16,18-29]

Trends in Medication Usage and Costs

The IMS Institute for Healthcare Informatics reported that in 2014, US spending on prescription drugs, after many years of slowing growth, saw the largest spending increase since 2001, with the cost rising 13.1% over 2013 to reach $373.9 billion. This increase is attributed not only to a rise in utilization of specialty medicines, but also to innovation. A record-breaking number of FDA marketing approvals has resulted in many new medicines, a large proportion of which occupy specialty therapy areas that include oncology, hepatitis C, and auto-immune diseases, which collectively accounted for $34.7 billion of drug expenditures in 2014. Also in 2014, 10 first-in-class FDA-approved products designated as orphan drugs were launched for rare conditions such as homozygous familial hypercholesterolemia, idiopathic PAH, Gaucher's disease, and several types of hemophilia, making new, effective drug therapies available to people diagnosed with rare and neglected diseases.[34]

Because of this continued increase in specialty drug spending, along with the continued growth of an aging population that uses proportionately more prescription drugs, managed care decision makers are tasked with making policy decisions that consider the use of utilization management tools in order to bring high value to their members. Utilization management tools include strategies such as step edits, prior authorization, and restrictions on combination therapy, among others.

Figure 1. Target Pathways and Current Therapies in Pulmonary Arterial Hypertension[14,15]



cAMP indicates cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; sGC, soluble guanine cyclase.
Schematic diagram of 3 biologic pathways involved in the pathogenesis of pulmonary arterial hypertension.
Adapted from Humbert et al. *N Engl J Med.* 2004;351(14):1425-1436.

Before policy and formulary determination, decision makers must carefully consider clinical evidence in the form of RCTs, retrospective research, registry data, and expert guidelines in order to determine the value of a medication and its place in therapy.

Clinical Support for Combination Therapy

Proceedings From the World Symposium on Pulmonary Hypertension

In 1973, the first World Symposium on Pulmonary Hypertension (WSPH) was held in Geneva, Switzerland, in response to an epidemic of PAH caused by the anorexigenic medication Aminorex.[35] Twenty-five years later, at the time of the second WSPH, in Evian, France, there were only 2 effective treatments for PAH: the prostacyclin analogue epoprostenol, and high-dose calcium channel blockers for the relatively few patients who were responsive to acute vasoreactivity testing. The second symposium is widely regarded as the beginning of the modern era of treatment for PAH because it resulted in the creation of the first PAH treatment algorithm.[3,35]

At the time of the third WSPH (Venice, Italy) in 2003, 3 classes of PAH-specific drugs (ERAs, prostanoids, and PDE5 inhibitors) were available for treatment of PAH.[35]

Table 1. Advanced Therapy Agents Available in the United States for the Treatment of PAH[18-29]

Medication	Mechanism of Action	Method of Administration
Endothelin Pathway		
bosentan (Tracleer)	ERA	Oral tablet
ambrisentan (Letairis)	ERA	Oral tablet
macitentan (Opsumit)	ERA	Oral tablet
Nitric Oxide Pathway		
sildenafil (Revatio)	PDE5 inhibitor	Oral tablet
tadalafil (Adcirca)	PDE5 inhibitor	Oral tablet
riociguat (Adempas)	sGC stimulator	Oral tablet
Prostacyclin Pathway		
epoprostenol sodium (Flolan)	Prostanoid	Intravenous
epoprostenol (Veletri)	Prostanoid	Intravenous
treprostinil (Tyvaso, Remodulin, Orenitram)	Prostanoid	Inhaled, intravenous/subcutaneous, oral tablet
iloprost (Ventavis)	Prostanoid	Inhaled

ERA indicates endothelin receptor antagonist; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase-5; sGC, soluble guanylate cyclase.

The proceedings of this symposium classified combination therapies as experimental for patients who failed to show improvement or who displayed deteriorated health with earlier treatment. A supplemental publication opined that, provided that additional confirmatory evidence was obtained, combination therapy would in the future become an early-line therapy.[12,36]

It was not until 2008 that the fourth WSPH proceedings endorsed the consideration of combination therapy and goal-oriented treatment. Treatment algorithms developed at the fourth (2008) and fifth (2013) WSPHs delineated the role of the PAH-approved therapies described herein, as well as supportive therapies including supplemental oxygen, diuretics, digitalis, and anticoagulants.[3,7] Table 2[3] shows the 2013 evidence-based treatment algorithm for initial therapy for PAH with approved drugs. In patients with inadequate clinical response to monotherapy with a PAH-approved therapy, combination therapy is allocated a grade of recommendation I and level of evidence A. For patients in functional class (FC) III or IV, initial combination therapy is allocated a grade of recommendation IIb and level of evidence C (Table 2 and Table 3).[3] The current algorithm recommends the sequential introduction of combination therapy. However, data from newer clinical trials may provide evidence supporting use of initial combination therapy for treatment-naïve patients.[3,15] Before the fifth WSPH proceedings were published, providers utilized combination therapy when treatment goals were not met, and a body of clinical trials evidence with combination therapy in PAH has been developed.

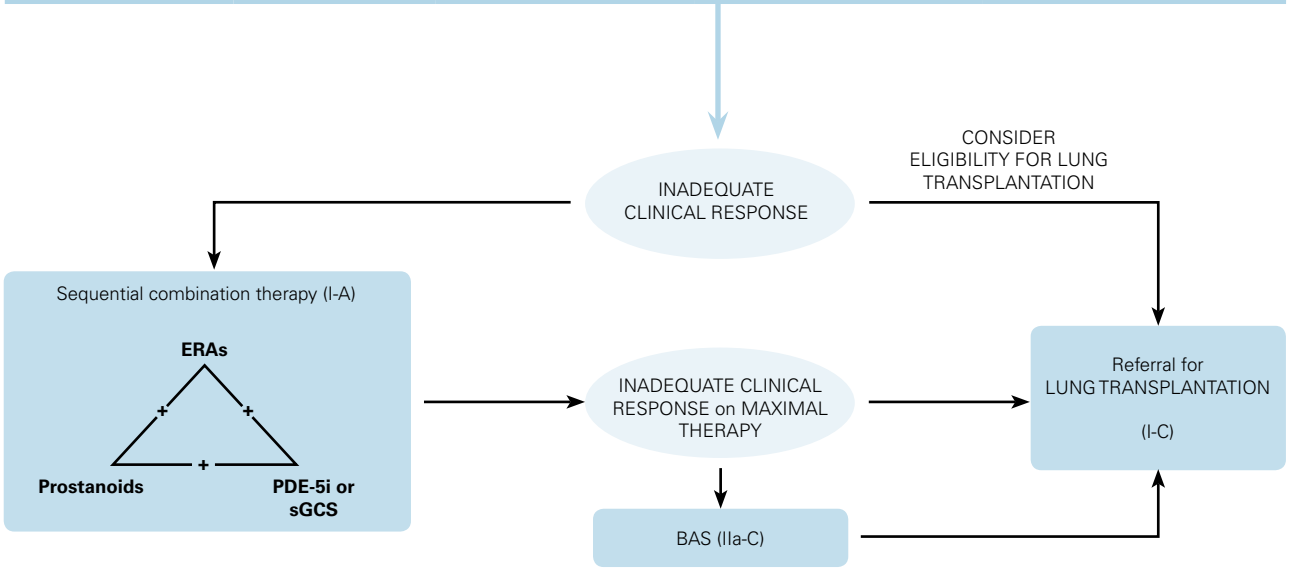
Evolving Clinical Evidence

In 2003, BREATHE-2, a small RCT to assess the safety and efficacy of bosentan combined with epoprostenol for patients in FC III & IV, was reported. Results showed a promising but nonsignificant trend toward greater improvement in hemodynamic parameters. PAH-associated serious adverse events were similar for both treatment arms. In the 12-week STEP trial, which was primarily a safety trial with secondary efficacy end points, iloprost was added to patients on stable bosentan therapy. Safety data were consistent with previous trial experience, and comparable efficacy was demonstrated (time to clinical worsening [TTCW], FC, and hemodynamics). Table 4[22,32,37-52] provides study experience with combination therapy trials. A meta-analysis of 6 trials also confirmed the efficacy and safety of combination therapy. Compared with the control group, combination therapy reduced the risk of clinical worsening (relative risk [RR], 0.48; 95% CI, 0.26-0.91; P = 0.023); increased the 6-minute walk distance (6MWD) significantly (22 m); and reduced the mean pulmonary arterial pressure, right atrial pressure, and PVR. The incidence of serious adverse events was not significantly different between combination therapy and monotherapy (RR, 1.17; 95% CI, 0.40-3.42; P = .77).[3]

A treatment strategy trial involving combination ther-

Table 2. Evidence-Based Treatment Algorithm for Initial Therapy With PAH-Approved Drugs for Nonvasoreactive Patients, From the World Health Organization[3]

Recommendation	Evidence[a]	WHO-FC II	WHO-FC III	WHO-FC IV
I	A or B	ambrisentan bosentan macitentan riociguat sildenafil tadalafil	ambrisentan bosentan epoprostenol IV iloprost inhaled macitentan riociguat sildenafil tadalafil treprostinil SC, inhaled	epoprostenol IV
IIa	C		iloprost IV[b] treprostinil IV	ambrisentan bosentan iloprost inhaled and IV macitentan riociguat sildenafil tadalafil treprostinil SC, IV, inhaled
IIb	B		beraprost[b]	
	C		Initial combination therapy	Initial combination therapy



Red highlights: morbidity and mortality as primary end point in randomized controlled study or reduction in all-cause mortality (prospectively defined).

BAS indicates balloon atrial septostomy; ERA, endothelin receptor antagonist; IV, intravenous; PAH, pulmonary arterial hypertension; PDE-5i, phosphodiesterase type-5 inhibitor; SC, subcutaneous; sGCS, soluble guanylate cyclase stimulator; WHO-FC, World Health Organization functional class.

[a]The levels of evidence supporting the recommendations are as follows:

- Level A evidence is supported by multiple randomized controlled trials (RCTs) or meta-analysis data. It is important to note that findings of clinical trials that are not based on prospectively defined end points (eg, post hoc analyses or subgroup analyses) do not constitute level A evidence.
- Level B evidence is supported by a single RCT or a large nonrandomized study or studies.
- Level C evidence is the least reliable form of evidence. Evidence in level C may be based on a consensus of opinion among experts, small studies, or both. Findings of retrospective studies and registry studies are also in the category of level C evidence.

[b]Only approved in Japan and South Korea (beraprost) and in New Zealand (iloprost IV).

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Table 3. WSPH Treatment Algorithm Recommendation Classes and Levels of Evidence[3]

Recommendation Class		
Class	**Definition**	**Suggested Wording**
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and may in some cases be harmful	Is not recommended
Level of Evidence[a]		
Level	**Definition**	
A	Data derived from multiple randomized clinical trials or meta-analyses	
B	Data derived from a single randomized clinical trial or large nonrandomized studies	
C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries	

WSPH indicates World Symposium on Pulmonary Hypertension.
[a]Results on the basis of post hoc and subgroup analyses of clinical trials most often do not meet the criteria of level of evidence A.
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apy was published by Hoeper and colleagues in 2005. This study assessed a combination of bosentan and sildenafil, and in cases where treatment goals were not reached, the addition of inhaled iloprost. Comparisons with a historical control group suggested a lengthened survival time with combination therapy, but could not definitively confirm that combination therapy was superior to monotherapy. The authors concluded that prospective controlled trials were needed to address this question.[53]

By 2008, additional RCTs utilizing combination therapy had been conducted (Table 4).[22,32,37-52] PACES was the first PAH combination therapy study of significant size (N = 267). In the PACES trial, the effect of adding oral sildenafil to long-term intravenous (IV) epoprostenol in patients with PAH was studied over the course of the 16-week trial. Patients were randomly assigned to receive placebo or sildenafil titrated up to 80 mg 3 times daily (4 times higher than the FDA-approved dosage). A placebo-adjusted increase from baseline of 28.8 meters (95% CI, 13.9-43.8; $P = .001$) in the 6MWD was seen in patients in the sildenafil group. The addition of sildenafil to stable long-term IV epoprostenol therapy resulted in improvements in exercise capacity, hemodynamic parameters, TTCW, and quality of life, but not Borg dyspnea score. Increased rates of headache and dyspepsia occurred with the addition of sildenafil.[42]

A more recent registration trial, PATENT-1, assessed the efficacy and safety of riociguat in PAH patients. The study included both treatment-naïve patients and those treated with an ERA or an oral, inhaled, or subcutaneous prostanoid. A statistically significant improvement in 6MWD was seen both for patients treated with riociguat monotherapy (38 meters from baseline [95% CI, 15-62 meters]) and those on combination treatment (36 meters from baseline [95% CI, 15-56 meters]). Riociguat was well tolerated, with a discontinuation rate of 3% in the 2.5 mg–maximum dose group versus 7% in the placebo group.[32,54]

Not all trials with combination therapy have met primary efficacy end points. Two trials, FREEDOM-C and FREEDOM-C2, utilized oral treprostinil added to stable doses of an ERA and/or PDE5 inhibitor. The primary end point, an improvement in 6MWD, was not met with statistical significance in either trial.[45,46]

Importantly, some of the more recent trials have moved away from the functional end point, change in 6MWD, to a composite primary end point that more clearly reflects the progression of the disease. In the late 1990s, Dr Bob Temple of the FDA advocated for meaningful end points in clinical trials. He defined meaningful end points as direct measures of how a patient feels, functions, or survives, with function referring to the ability of a patient to carry out normal daily activities.[55] More recently, in the proceedings of the fifth WSPH, the experts recommended TTCW as an appropriate end point in registration trials and proposed an array of similarly themed clinical end points, including all-cause death, lung transplantation, hospitalization for worsen-

Table 4. Combination Therapy Trials in Pulmonary Arterial Hypertension[22,32,37-52]

Trial	Duration	Number of Patients	Drugs Involved	Efficacy Data	Safety Data
STEP	12 weeks	iloprost (n = 34) placebo (n = 33)	background bosentan (≥4 months) + iloprost inhalation vs placebo	improvement in 6MWD with combination therapy vs placebo (~26 m) (P = .051)	discontinuations due to AEs: 1 iloprost, 1 placebo
COMPASS-1	measurement of PVR 1 hour after administration	sildenafil (n = 45)	background bosentan (≥12 weeks) + sildenafil 25 mg	reduction in PVR (mean change –15%) (P <.0001) TPR reduction (–13%)	0% serious adverse events observed; safety of treatment arms comparable
BREATHE-2	16 weeks	bosentan (n = 22) placebo (n = 11)	background epoprostenol (2 days) + bosentan vs placebo	TPR reduction (–36.3% vs placebo –22.6%) (P = .08) non–statistically significant trend toward improved hemodynamic parameters	discontinuations due to AEs: 2 patients, 1 in each treatment group (bosentan/epoprostenol, placebo/epoprostenol)
PACES	16 weeks	sildenafil (n = 134) placebo (n = 133)	background epoprostenol (≥3 months) + sildenafil vs placebo	increase in 6MWD (~29.8 m) (P <.001) clinical worsening in 6.2% of patients receiving sildenafil vs 19.5% of patients receiving placebo (P = .002)	discontinuations due to AEs: 14 (11%) patients in the placebo group and 7 (5%) patients in the sildenafil group
PHIRST	16 weeks	treatment-naïve + tadalafil (n = 74) vs treatment naïve + placebo (n = 37) vs background bosentan + tadalafil (n = 87) vs background bosentan + placebo (n = 45)[a]	treatment-naïve or background bosentan + tadalafil or placebo	tadalafil 40 mg improved placebo-adjusted 6MWD by 44 m (P <.01) at week 16 in treatment-naïve patients	discontinuations due to AEs: 16%; similar across all treatment groups
TRIUMPH-1	12 weeks	inhaled treprostinil (n = 115) placebo (n = 120)	bosentan (70%) or sildenafil (30%) + inhaled treprostinil or placebo	improved 6MWD (~20 m) (P = .0004)	discontinuations due to AEs: treprostinil 7 patients; placebo 4; 1 death[b]
FREEDOM-C	16 weeks	350 patients	patients on stable doses of ERA, PDE5, or both received oral treprostinil or placebo	nonsignificant for primary end point of 6MWD	discontinuations due to AEs: 14% oral treprostinil; 5% placebo
FREEDOM-C2	16 weeks	310 patients; oral treprostinil (n = 157), placebo (n = 153)	patients on stable doses of ERA, PDE5, or both received oral treprostinil or placebo	nonsignificant for primary end point of 6MWD	discontinuations due to AEs: 11% oral treprostinil; 3% placebo
PATENT-1	12 weeks	443 patients	randomized to riociguat or placebo; 44% of patients on ERAs, 6% of patients on non-intravenous prostanoids	36 m placebo-adjusted improvement in 6MWD (P <.001)	discontinuations due to AEs: 3% riociguat; 7% placebo

Continued on next page

Table 4. Combination Therapy Trials in Pulmonary Arterial Hypertension (Continued)[22,32,37-52]

Studies With Morbidity/Mortality End Point[c]					
Trial	**Duration**	**Number of Patients**	**Drugs Involved**	**Efficacy Data**	**Safety Data**
COMPASS-2	7.2 years	bosentan (n = 159) placebo (n = 175)	bosentan + sildenafil vs sildenafil + placebo	Primary end point not met. Time to M/M event was not prolonged 17% risk reduction for time to first morbidity/mortality event (P = .25)	no new safety signals observed
SERAPHIN	3.8 years	macitentan (n = 492) placebo (n = 250)	3 or 10 mg macitentan vs placebo (63.7% receiving study drug in combination with other therapy—PDE5, inhaled or oral prostanoid)	macitentan 10 mg reduced risk of M/M event 45% overall risk reduction of M/M event (P <.001)	discontinuations due to AEs: 10.7% macitentan 10 mg; 12.4% placebo
GRIPHON	4.3 years	1156 patients	selexipag (80% combinations with ERA, PDE5, or both)	40% risk reduction of M/M event (P <.0001)	discontinuations due to AEs: 14.3% selexipag; 7.1% placebo
AMBITION	3.7 years	tadalafil + ambrisentan (n = 302) ambrisentan (n = 152) tadalafil (n = 151)	tadalafil + ambrisentan in treatment-naïve patients vs monotherapy with either agent	50% reduced risk of clinical failure (P = .0002)	discontinuations due to AEs: 9% combination; 12% pooled mono

AE indicates adverse event; ERA, endothelin receptor antagonist; M/M, morbidity/mortality; PDE5, phosphodiesterase-5; PVR, pulmonary vascular resistance; 6MWD, 6-minute walk distance; TPR, total pulmonary resistance.
[a]All patient numbers are for data shown, not total patients in study.
[b]In an open-label extension study, the safety of the combination therapy was demonstrated over 2 years of follow-up.
[c]SERAPHIN is published data; COMPASS-2, GRIPHON, and AMBITION data are from abstracts and press releases.

ing PAH (including atrial septostomy), initiation of IV therapy due to worsening PAH, worsening of function (ie, worsening FC and exercise capacity), and worsening of PAH symptoms (eg, worsening of at least 2 of the 4 symptoms: dyspnea, chest pain, dizziness/syncope, and fatigue/activity level).[56]

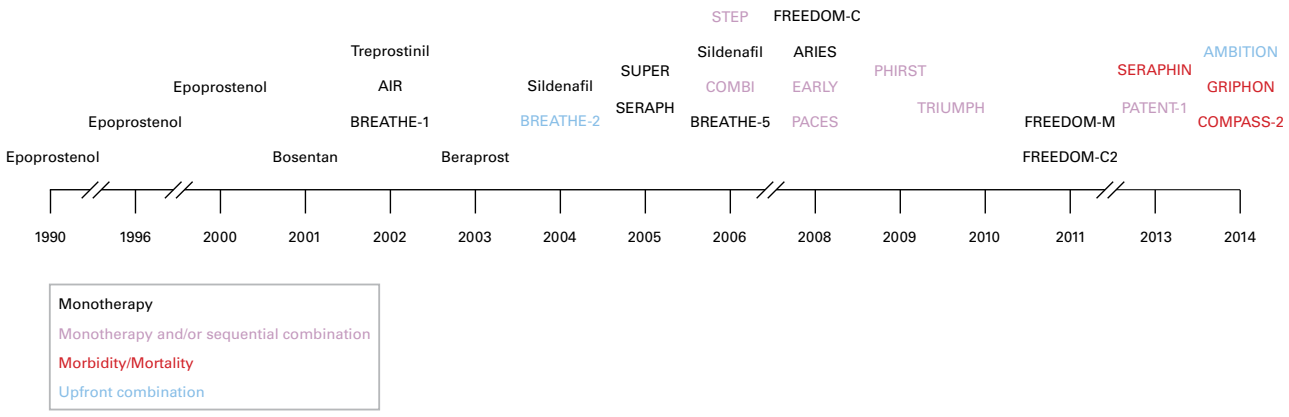
COMPASS-2, a combination trial using sequential therapy with sildenafil and bosentan, was the earliest PAH trial with a primary morbidity/mortality (M/M) end point. COMPASS-2 began in 2006 and ended in 2013 (Table 4).[22,32,37-52] The trial, although important as the first PAH M/M trial, did not reach its primary end point, as the observed risk reduction for patients treated with bosentan as an add-on to sildenafil was not a statistically significant difference at 17% versus placebo (hazard ratio, 0.83; P = .25). No new safety signals were revealed in the long-term trial (median duration, 22.7 months).[47,57]

The first completed event-driven RCT with an M/M end point in PAH to show a significant difference between treatment arms was the SERAPHIN trial, in which macitentan (3 mg and 10 mg) was assessed in a long-term trial. The median treatment period of 115 weeks allowed evaluation of the drug on disease progression. Approximately two-thirds of patients were already on a PAH-approved therapy at enrollment (61.4% on a PDE5-type inhibitor and 5.4% on oral or inhaled prostanoid). Macitentan 10 mg significantly reduced the risk of an M/M event by 45% (P <.001) overall (55% for treatment-naïve patients, 38% for patients on combination therapy). The risk of the secondary composite end point of PAH-related death or hospitalization was reduced by 50% (97.5% CI, 0.34-0.75; P <.001).[22,48]

Two additional M/M trials utilizing combination therapy have recently been reported. The GRIPHON study assessed the safety and efficacy of an investigational drug, selexipag (ACT-293987), in the largest PAH M/M trial to date (N = 1156), spanning 4.3 years. Eighty percent of patients enrolled were already on a background regimen of 1 or 2 PAH-approved drug therapies (ERA, PDE5). Selexipag decreased the risk of an M/M event versus placebo by 40% (P <.001).[49,50] This effect was consistent for patients on monotherapy and on combination therapy.

Lastly, the event-driven treatment-strategy trial AMBITION assessed the safety and efficacy of initial

Figure 2. Historical Timeline of Combination Therapy Trials[5,32,45-52,57]



Randomized controlled studies in pulmonary arterial hypertension are identified by acronyms, if any, or drug name, and year of publication. Adapted from Galiè et al. *Eur Heart J.* 2010;31(17):2080-2086.

combination therapy with tadalafil and ambrisentan versus pooled monotherapy in treatment-naïve incident patients. The top line results demonstrated a 50% (P = .0002) risk reduction of clinical failure with initial combination therapy compared with pooled groups of patients taking either medication alone.[51,52] Figure 2[5,32,45-52,57] contains a timeline of combination therapy trials, and Table 4[22,32,37-52] presents results of recent combination trials.

Concomitant with the growing body of evidence, the FDA has recently acknowledged the role of combination therapy in the labeling for newer PAH therapies. For example, in the prescribing information for 2 new drugs approved in 2013, Adempas (riociguat) and Opsumit (macitentan), the usage statements mention that these agents have demonstrated efficacy in combination with other approved PAH therapy.[19,22]

Combination Therapy Use in Other Chronic Conditions

Combination therapy in PAH has followed the pattern of combination therapy in other chronic conditions, where multiple agents targeting distinct pathways have demonstrated efficacy and safety. The evolution of combination therapy in heart failure (HF) is analogous to current trends in PAH treatment. Early trials in HF, such as CONSENSUS, demonstrated the benefit of enalapril monotherapy. Subsequently, the added benefit of enalapril with a background diuretic and digoxin therapy was confirmed in a clinical trial (SOLVD).[58,59] With the addition of beta-blockers, evidenced by positive results in the CIBIS-II and COMET trials, other combinations became standards of care.[60,61] More recently, HF trials have demonstrated the benefit of treatment regimens that include still other agents targeting additional pathways.[62,63] It is now common practice in HF therapy to utilize a combination regimen with several agents targeting different pathways.[64] Similar patterns are seen in the treatment of other chronic diseases, such as diabetes, systemic hypertension, and cancer.

Conclusion

Combination therapy has the potential to become the standard of care for PAH patients. Experience with combination therapy in the treatment of PAH demonstrated through a decade of clinical trials has shown benefit. Real-world data from the REVEAL registry suggest that combination therapy in PAH has become prevalent in treatment regimens in the United States and that morbidity may have been positively impacted. Recent M/M trials such as SERAPHIN and GRIPHON provide evidence of clinical benefit of combination therapy across a broad spectrum of patients with PAH. Adoption of initial combination therapy could be near, as clinical practice may reflect the initial combination treatment strategy recently

demonstrated in AMBITION. The new European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines will be presented and published at the ESC Congress later in 2015, and it is likely that initial combination therapy will be among the recommendations.

Rare and deadly diseases such as PAH that require high-touch, high-management specialty medications remain on the radar as health plans aim to control costs while improving the quality of care for their members. In pursuit of providing the greatest value and benefit to the majority of the PAH patient population, decision makers must be able to assess these specialty medications with the help of clinical evidence from RCTs, retrospective research, registry data, and expert guidelines. They must weigh the benefit of improved outcomes for patients, and reduction in resource-intensive events (morbidity, hospitalization), against the associated costs. This article has provided support for managed care decision makers as they evaluate combination therapy in PAH.

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