# The Evolution of Prostacyclins in Pulmonary Arterial Hypertension: From Classical Treatment to Modern Management

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Two decades have passed since the approval of the first prostacyclin for the treatment of pulmonary arterial hypertension (PAH).[1] However, managed care decision makers have little experience with these treatments, in part due to the rarity of PAH. The disease has a prevalence of 15 to 50 cases per million individuals worldwide, with an incidence and prevalence in the United States estimated at 2.3 and 12.4 cases per million individuals, respectively.[2-4] Prostacyclins have typically been covered under the insurance medical benefit because they require durable medical equipment and are administered by an intravenous, subcutaneous, or inhalation route. As a result, this class of medications may be less familiar to managed care decision makers.[5]



Consequently, knowledge of prostacyclin and prostacyclin analog indications, dosing, and administration logistics among decision makers in managed care remains limited. The complexity and expense of drug delivery must be appreciated. In addition, the number and type of prostacyclin options continue to expand. An oral formulation was approved in 2013,[6] and a selective IP prostacyclin receptor agonist was recently approved by the FDA.[7] The expanded choices targeting the prostacyclin pathway add to the challenge for managed care decision makers. To evaluate new treatment options and arrive at clinically sound and cost-effective treatment decisions, an improved understanding of these drugs is needed and will be the focus of this review.

PAH is a subset of a group of diseases known as pulmonary hypertension (PH). PH is classified into 5 categories (Table[8]).[8] World Health Organization (WHO) group 1 PAH comprises several etiologies. Notably, in the Registry to Evaluate Early And Long-term PAH Disease Management (REVEAL) study, results showed that the cause of group 1 PAH was idiopathic in approximately half (46.2%) of nearly 3000 enrolled patients.[9]

**Abstract**

Prostacyclins for the treatment of pulmonary arterial hypertension (PAH) have historically been covered under the insurance medical benefit because they require durable medical equipment and are administered by an intravenous, subcutaneous, or inhalation route. However, more treatment options that target the prostacyclin pathway have become available. As the number and type of options expand, an improved understanding of these drugs will aid managed care decision makers in evaluating new treatment options and making clinically sound and cost-effective treatment decisions. PAH is a progressive disease of pulmonary vascular remodeling that increases pulmonary vascular resistance and often results in right-side heart failure and death if left untreated. Adverse event profiles, the complexity of administration modalities, and potential complications must be considered when administering prostacyclin therapy. Traditional modes of administration, with their potential challenges and complications, may have contributed to the unmet need for an oral agent. Another consideration for managed care decision makers is that oral agents are generally covered under the insurance pharmacy benefit. Access to oral medications with long-term outcomes data, as well as the improved convenience of oral therapy, may help patients with PAH maximize function by maintaining a more convenient and consistent therapeutic regimen.

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For author information and disclosures, see end of text.

**Table.** Classification of Pulmonary Hypertension[8]

| Group | Specific Condition Name(s) | Associated Conditions |
|---|---|---|
| 1 | PAH | Idiopathic, heritable, drug/toxin-induced, associated with another condition (eg, connective tissue disease) |
| 1′ | Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis | N/A |
| 1″ | Persistent pulmonary hypertension of the newborn | |
| 2 | PH due to left-side heart disease | Systolic dysfunction, diastolic dysfunction, valvular disease |
| 3 | PH due to lung disease and/or hypoxia | Several diseases may precipitate group 3 PH, including COPD and ILD |
| 4 | CTEPH | May be precipitated by pulmonary embolism |
| 5 | PH with unclear/multifactorial mechanisms | Several diseases may precipitate group 5 PH, including hematologic/systemic/metabolic disorders |

COPD indicates chronic obstructive pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; ′, prime; ″, double prime.
Adapted from Simonneau et al. *J Am Coll Cardiol.* 2013;62(suppl 25):D34-D41.

PAH is a progressive disease of pulmonary vascular remodeling that increases pulmonary vascular resistance and often results in right-side heart failure and death.[10] Patients present with symptoms such as dyspnea, chest pain, fatigue, or syncope.[11] The symptom complex results in deterioration of exercise capacity and functional status, both of which are graded by a modified New York Heart Association or WHO functional class (FC) ranging from I (minimal or no symptoms) to IV (symptoms at rest or syncope). The nonspecific nature of the symptoms and the complexity of the diagnosis often lead to diagnostic delay. On average, 2.8 years elapse between the onset of symptoms and a confirmed diagnosis of PAH.[9]

Echocardiography is generally used to screen for PH, but a right-side heart catheterization is necessary for a definitive diagnosis.[12] Hemodynamically, PAH is defined as a mean pulmonary artery pressure ≥25 mm Hg, a pulmonary artery wedge pressure ≤15 mm Hg, and a peripheral vascular resistance >3 Wood units.[13]

## The Causes of PAH

The causes of PAH are not fully characterized, leading scientists to believe they are multifactorial.[3,14] An imbalance of vasoactive mediators is pivotal. There is impaired production of the endogenous vasodilators prostacyclin and nitric oxide and enhanced production of the vasoconstrictive mediators thromboxane A2 and endothelin.[3,15] In addition, endothelial cell dysfunction plays a key role in PAH pathogenesis. Tissue remodeling, proinflammatory signaling, and several other relevant pathways in PAH pathogenesis may contribute to defects of endothelial cell function.[16] Within the endothelial cell, approved PAH-specific therapies target 3 discrete pharmacologic pathways: the endothelin pathway, the nitric oxide pathway, and the prostacyclin pathway (**Figure 1**[17,18]).[15]

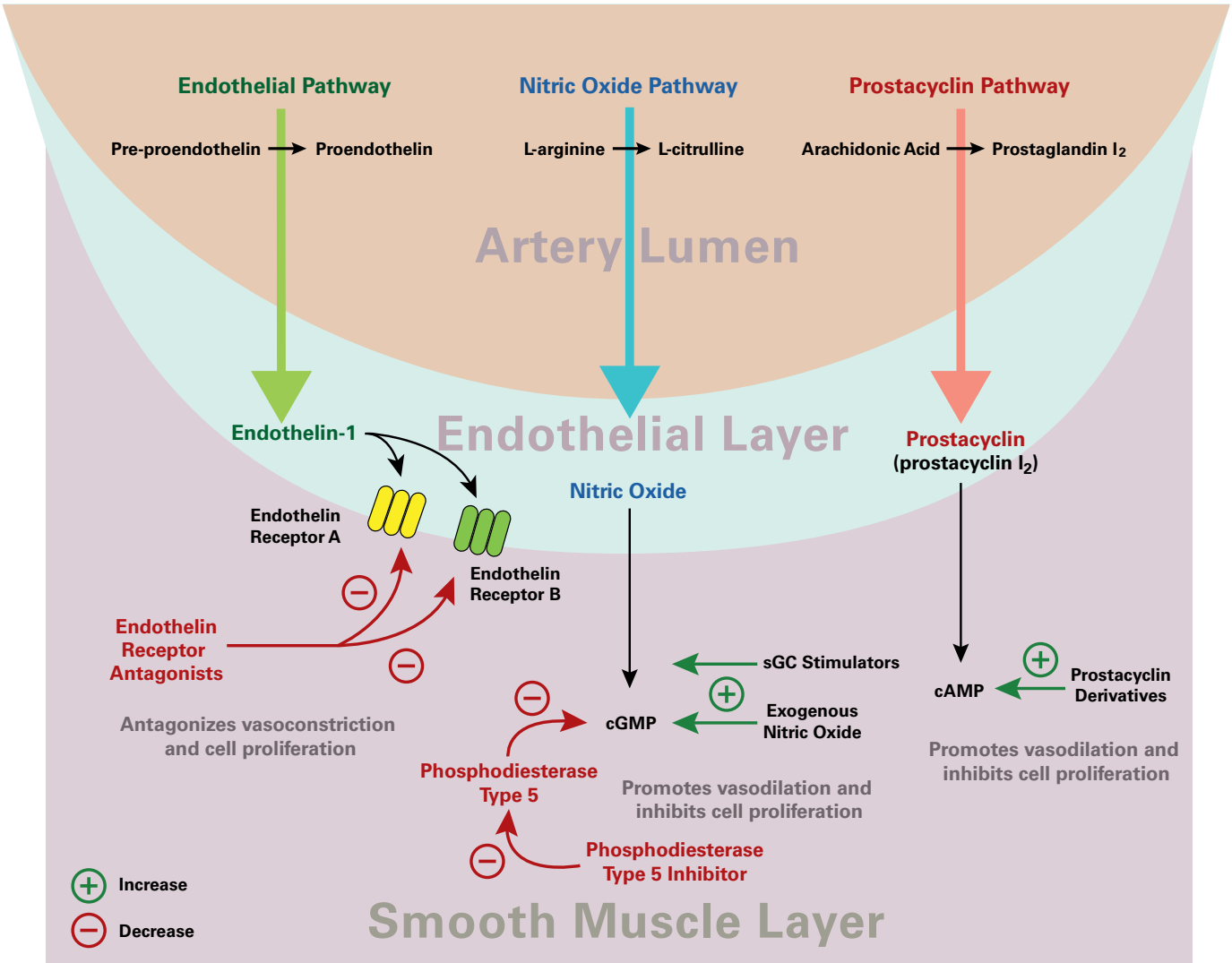
## Targeted Therapy for PAH

The currently available agents approved by the FDA encompass 3 classes: prostanoids (which will be discussed in more detail), endothelin-receptor antagonists (ERAs), and those that affect nitric oxide (ie, phosphodiesterase-5 [PDE5] inhibitors and a soluble guanylate cyclase [sGC] stimulator). The ERAs include the oral treatments ambrisentan, bosentan, and macitentan. Sildenafil (oral and for short-term intravenous use during hospitalization) and tadalafil (oral) are PDE5 inhibitors approved for use in PAH. Finally, the oral sGC stimulator riociguat enhances endogenous nitric oxide signaling, independent of baseline endogenous nitric oxide levels.[15,17,19-24]

The 2013 WHO treatment algorithm developed at the World Symposium on Pulmonary Hypertension (WSPH) held in Nice, France, relies on WHO FC for specific drug choice (**Figure 2**[15]). In general, for patients with more limited symptoms (ie, WHO FC II), oral therapies are recommended, while intravenous prostanoids are recommended for those with more severe disease (WHO FC IV). For WHO FC III, all approved medical therapies may be considered. Without head-to-head drug comparisons, any drug with evidence for efficacy is listed as an option, with the specific selection left to the clinician.

Prostanoid therapy is supported by evidence-based guidelines for both WHO FC III and IV patients and is

**Figure 1.** Target Pathways and Current Therapies in Pulmonary Arterial Hypertension[17,18]



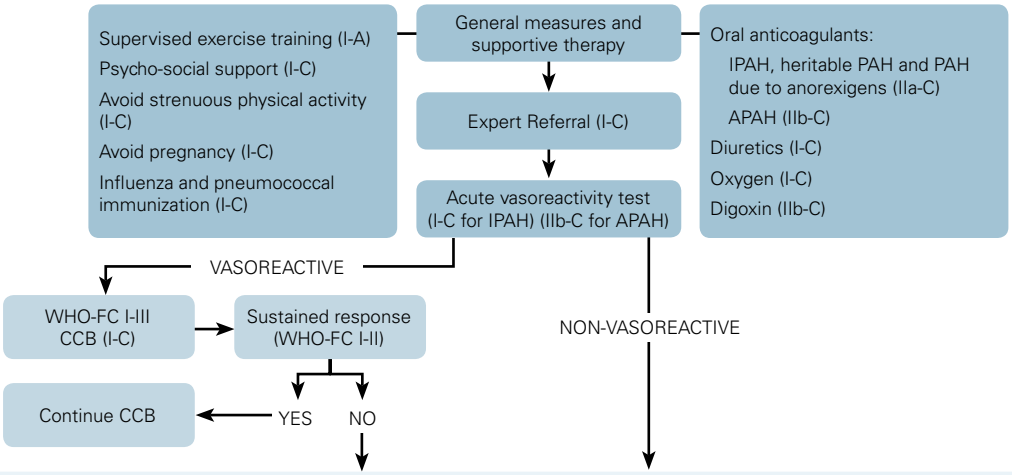

cAMP indicates cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; sGC, soluble guanine cyclase.
Schematic diagram of 3 biologic pathways involved in the pathogenesis of pulmonary arterial hypertension.
Adapted from Humbert et al. *N Engl J Med.* 2004;351(14):1425-1436.

the cornerstone for FC IV.[15] Prostanoids have historically been added as sequential therapy in combination with oral medication in patients with poor response or severe PAH. This approach has largely been based on the complexity of administration of prostanoids. However, the availability of oral prostanoid preparations introduces the possibility that these agents may be added earlier in the treatment course as evidence mounts that combination therapy significantly reduces PAH morbidity.[25-27]

### *Combination Therapy*

The 2013 WHO algorithm recommends prostanoids in combination with a separate drug class for patients with inadequate initial response to monotherapy with a grade I, evidence level A/B recommendation.[15] However, for more than a decade, real-world treatment has included initial combination as a therapeutic strategy in PAH.[3,26] In addition, nearly half (43%) of all trials evaluating PAH-specific therapies include at least one subgroup of patients receiving combination therapy. Common

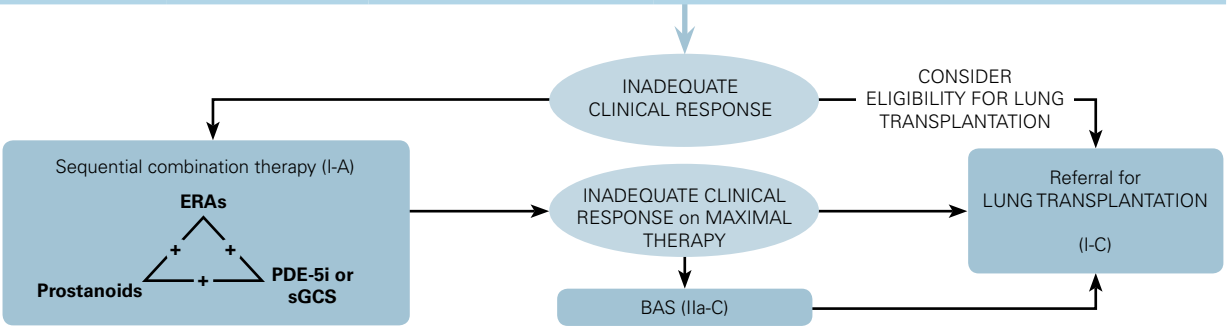
**Figure 2.** Treatment Algorithm in Pulmonary Arterial Hypertension[15]




Initial Therapy With PAH-Approved Drugs

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

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




APAH indicates associated pulmonary arterial hypertension; BAS, balloon atrial septostomy; CCB, calcium channel blockers; ERA, endothelin receptor antagonist; IPAH, idiopathic pulmonary arterial hypertension; 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]Level of evidence is based on the WHO-FC of the majority of the patients of the studies.

[b]Approved only by the FDA (macitentan, riociguat, treprostinil inhaled); in New Zealand (iloprost IV); in Japan and South Korea (beraprost).

[c]Positive opinion for approval of the Committee for Medicinal Products for Human Use of the European Medicines Agency.

From WHO 2013 World Symposium on Pulmonary Hypertension proceedings held in Nice, France.

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combination treatments include ERA/PDE5 inhibitor therapy, ERA/prostanoid therapy, and prostanoid/PDE5 inhibitor therapy.[15]

Until recently, level A evidence for upfront combination therapy was lacking[25-27]; therefore, the recommendation was limited to sequential therapy for those patients not responding to initial therapy. Results from the recently published Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) study demonstrated the efficacy of initial ERA/PDE5 inhibitor combination therapy over monotherapy with either drug alone in reducing a composite morbidity/mortality outcome in PAH patients with WHO FC III or IV symptoms (HR, 0.50; 95% CI, 0.35-0.72). This composite end point included death, hospitalization due to worsening of PAH, disease progression, or suboptimal long-term clinical response to therapy.[27] The AMBITION results led to a new FDA-approved indication for combination therapy with these 2 agents.[23]

The recently published European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines recommend 6 treatment regimens in initial combination therapy for PAH (eg, ambrisentan plus tadalafil for FC II and III disease, and bosentan plus intravenous epoprostenol for FC IV disease). Additionally, more than 10 options for sequential combination therapy in patients with WHO FC II, III, or IV disease were listed (eg, macitentan added to sildenafil, riociguat added to bosentan, or selexipag added to ERA ± PDE5 inhibitor therapy for FC II and III disease). These recently updated European treatment algorithms may reflect future revisions to other PAH-specific management algorithms.[28]

### *Prostacyclin Historical Perspective*

PAH was first described as a clinical entity in 1891, but it was not until 1995 that the first disease-specific therapy for PAH became available.[29,30] The more than 100-year lag between identification and availability of the first disease-specific treatment for PAH may have been due to limited availability of diagnostic technology such as right-side heart catheterization, disease rarity, and lack of research. The need for clinical and scientific advancement was emphasized in the late 1960s by an epidemic of PAH produced by a dietary suppressant (aminorex) prescribed for weight loss.[30] PAH developed in 0.2% of patients receiving aminorex.[29,31]

The increase in the number of newly diagnosed patients with PAH led to growing research interest in the disease. The need to accelerate the clinical and research knowledge of PAH resulted in the first WSPH in 1973, held by the WHO in Geneva, Switzerland.[29] At that 1973 inaugural event, experts in PAH gathered to discuss and update current knowledge and identify those areas requiring future research. Subsequent World Symposia have occurred in 1998 (Evian, France), 2003 (Venice, Italy), 2008 (Dana Point, California), and 2013 (Nice, France).[15]

A pivotal point in the development of treatments for the disease was approval of the first PAH-specific therapy, intravenous epoprostenol. Although epoprostenol was first used for treatment of PAH in 1984, it was not available commercially until 1995.[1,30,32] In 1984, Higenbottam and colleagues used intravenous epoprostenol in a young woman with severe WHO FC IV idiopathic PAH who had been bedridden for more than a year. Epoprostenol was originally intended as a bridge therapy while the patient awaited a lung transplant. However, the treatment resulted in clinical improvement beyond expectations. That experience was an important beginning in support of clinical trial development for epoprostenol.[30,32]

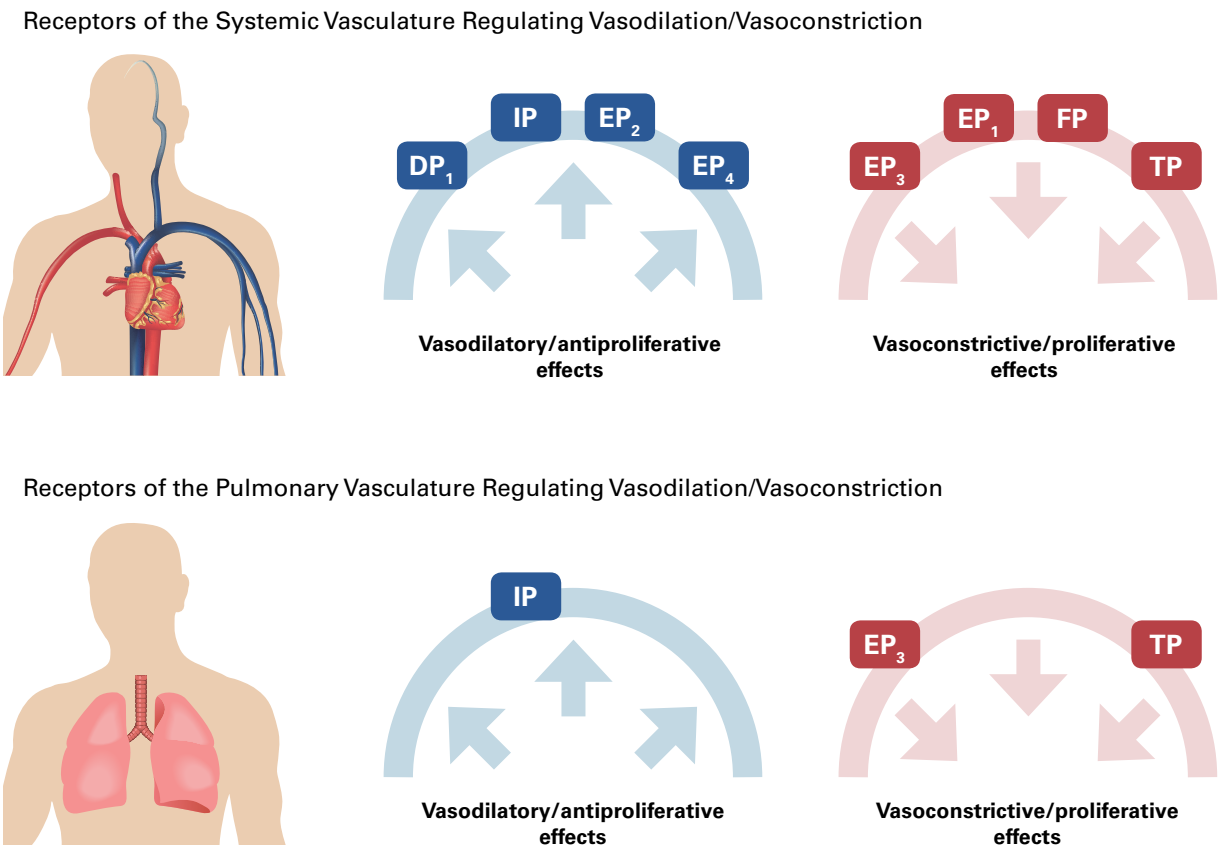
After the 1995 approval of epoprostenol for PAH, other prostanoids were introduced, including treprostinil for continuous subcutaneous infusion in 2002[33] and for continuous intravenous infusion in 2004.[34] Also in 2004, iloprost became the first prostacyclin analog approved for inhalation.[35] A second agent delivered by this route, the inhaled form of treprostinil,[36] was approved in 2009.[37] The oral form of treprostinil was approved in 2013[38] and, as of December 2015, the FDA approved a novel agent—the selective oral IP prostacyclin receptor agonist selexipag.[7]

## Prostacyclin Mechanism of Action

Prostacyclin, also called prostaglandin I2 (or PGI2), is an endogenous lipid molecule produced by endothelial cells. It is one of 5 principle bioactive prostanoids that act through 8 classical prostaglandin receptors.[39-42] Stimulation of receptors IP, $DP_1$, $EP_2$, and $EP_4$ promote relaxation of vascular smooth muscle.[39,43,44] For instance, prostacyclin interacts preferentially with the IP receptor, resulting in G protein activation, generation of the secondary messenger cyclic adenosine monophosphate, and specific target tissue effects.[39,41,45-47] Activation of these receptors leads to vasodilation, decreased cell proliferation, and inhibition of platelet aggregation.[43,48]

Several other receptors inhibit vasodilation or directly exert vasoconstrictive effects when stimulated. $EP_3$ is an inhibitory receptor; activation of this receptor leads predominantly to inhibition of smooth muscle relaxation, cell proliferation, and platelet aggregation.

**Figure 3.** Variable Effects of Prostanoids on Specific Receptor Subtypes[39,41,43,48]




In contrast, $EP_1$, FP, and TP stimulate smooth muscle cell contraction, directly resulting in vasoconstriction, cell proliferation, and platelet aggregation.[39] Endogenous prostanoids preferentially stimulate their specific receptors; however, prostanoids display substantial cross-reactivity across receptor subtypes.[40]

Within the lung, IP stimulation is especially important in promoting vasodilation, while $EP_3$ and TP are the primary pulmonary receptors involved in vasoconstriction (Figure 3[39,41,43,48]).[39,41,43,48] Receptor-specific compounds that mimic the desirable effects of endogenous prostacyclin on the cardiovascular system while minimizing the potential negative effects of cross-reactivity with vasoconstrictive receptors are preferable.[39,46,48]

## Formulation-Specific Characteristics

The pathobiology of PAH is complex, but it includes the key feature of prostacyclin deficiency. Replacing vasodilatory prostacyclin exogenously is a key treatment modality in patients with PAH. Specific features of available prostacyclin replacement therapy have clinically important implications.[3]

### *Prostacyclin Therapy—Parenteral and Inhaled*

Epoprostenol is the synthetic form of the naturally occurring prostaglandin derivative and is chemically identical to endogenous prostacyclin.[30] Traditionally, epoprostenol as first-line therapy has been reserved for patients with severe PAH (ie, patients with WHO FC III or IV disease).[4,15] Additionally, some data indicate the possible benefit of epoprostenol in the long-term prognosis of patients with disease regression and clinical improvement from FC III or IV to FC I or II after receiving prostacyclin therapy. This suggests that prostacyclin use in earlier stages of PAH may improve outcomes in some patients.[49-51]

Due to the extremely short half-life of epoprostenol (estimated at <6 minutes),[1,52] treatment must be administered continuously through an ambulatory infusion

pump connected to a permanent central venous access line. Emergency medical attention is required in cases of pump failure or loss of central venous access due to rapid drug elimination and possible life-threatening rebound worsening of the PAH.[4,15,30]

Epoprostenol is rapidly hydrolyzed and rendered inactive when administered orally and is unstable at physiologic pH. To ensure stability of the infusion formulation, the earliest approved form of epoprostenol (trade name: Flolan) is supplied as a freeze-dried lyophilized powder.[1] During preparation, this powder must be reconstituted and further diluted with an available proprietary diluent containing a glycine buffer, resulting in a final product for infusion that has a pH of 10.2 to 10.8.[1,30] The prepared solution may be stored for up to 40 hours under refrigeration and subsequently infused for up to 8 hours at room temperature. Cooling packs are required for administration beyond this 8-hour limit.[1] Home infusion of epoprostenol is administered with a CADD infusion pump; however, due to pump limitations, it is recommended that the drug solution be prepared and administered for 24 hours.[1,50,53,54]

In April 2010, a formulation of epoprostenol with improved thermal stability became available in the United States (trade name: Veletri). Veletri is stable without cooling packs for 48 to 72 hours, depending on concentration. At all concentrations, as outlined in the PI, Veletri, with a pH of 11 to 13, can be prepared and refrigerated for up to 8 days before use, allowing for less frequent product preparation and increased convenience for the patient.[15,52] Unlike Flolan, the buffer and osmotic agents that confer room-temperature stability characteristics of Veletri are contained within the drug vial.[55] Veletri can therefore be prepared with readily available sterile water for injection or normal saline, which provides cost advantages.[1,52]

Treprostinil (trade name: Remodulin) is a parenterally administered prostacyclin analog that has been chemically modified. Treprostinil is stable at room temperature, has an extended terminal elimination half-life of approximately 4 hours (following subcutaneous infusion). Subcutaneous formulations can be administered for up to 72 hours at temperatures up to 37°C (99°F). Intravenous infusion may be used if subcutaneous infusion is not tolerated and can be administered for up to 48 hours at temperatures as high as 40°C (104°F).[15,30,33]

Two inhaled formulations of prostacyclin are available in the United States. With inhaled iloprost (available since 2005 under the trade name Ventavis), treatment requires 6 to 9 administrations no more than every 2 hours during the day through the I-neb adaptive aerosol delivery system.[56] The other inhaled prostacyclin, treprostinil (available since 2009 under the trade name Tyvaso), requires 4 separate sessions spaced equally throughout the day, with inhalation through the TD-100 ultrasonic pulmonary delivery device. Each session may include as many as 9 inhalations, with dosage titration based on tolerability.[36]

## Prostacyclin Therapy: Challenges and Complications

The adverse event profiles, the complexity of administration modalities, and potential complications of these therapies must be considered when administering prostacyclin therapy.

### *Side Effects of Prostacyclins*

The most common side effects of parenteral prostacyclin therapies include dizziness, jaw pain, headache, musculoskeletal pain, nausea/vomiting, flu-like symptoms, and anxiety. Some adverse events, such as flushing, hypotension, chest pain, and tachycardia, may occur more frequently during initiation of treatment or after dosage adjustments.[1,33,52] Healthcare providers must manage these adverse events to reduce the risk of treatment discontinuation.[30,57]

### *Complications Associated With Modes of Administration*

Initiation of intravenous prostacyclin therapy may incur the additional cost of a hospital admission for placement of a central line, infusion initiation, and close monitoring during initial dosage titration.[1,30,33,52] Patients and caregivers require extensive education and practice to properly prepare and store medication while maintaining a 24-hour continuous infusion. With practice, preparation, which includes assemblage of necessary syringes and infusion pump cassettes; accurate reconstitution with the appropriate volume of solution; and assurance of proper storage, all while maintaining proper sterile technique, may be reduced to approximately 20 minutes per day.[30]

However, maintenance of proper administration technique with intravenous prostacyclins assumes that patients and caregivers:

- Have access to a reliable refrigerator or other controlled storage[4]
- Are capable of learning to mix and administer medication and do not have deficits of manual dexterity (manual dexterity issues often exist in patients with connective tissue disease and in elderly patients)[58]
- Are able to maintain central line hygiene to prevent local and systemic infections[30]

With any form of central venous access, a potential for bloodstream infection (BSI) exists with intravenous prostacyclin therapy.[1,33,52] With epoprostenol, BSIs due to sepsis have been estimated to occur at a rate of 0.3 events per patient per year.[1,52] Likewise, with intravenous treprostinil, the risk of BSIs has been estimated to average 1 event per 3 to 5 years of use.[33]

To minimize the risk of infection, healthcare professionals must educate patients and caregivers on the proper aseptic technique during preparation.[1,33,52] Patients and caregivers must also be prepared for failures of the central line or infusion pump, or inadequate medication supplies because even transient interruption of continuously infused prostacyclin therapies may lead to complications requiring urgent medical attention.[30]

Although continuous subcutaneous infusion of treprostinil may be preferable in some clinical situations because central venous access is not required,[33] infusion-site pain can be an important treatment-limiting side effect. Up to 85% of patients receiving subcutaneous infusion of treprostinil may experience serious infusion-site pain,[17] leading to treatment discontinuation in up to 23% of these patients.[58] In pivotal trials of subcutaneous treprostinil, nearly 32% of patients received prescriptions for narcotic pain relievers and 39% of patients experienced severe infusion-site pain, resulting in treatment discontinuation for 7% of all trial participants.[33] Because of these effects, treatment with subcutaneous treprostinil is generally not recommended for patients with a low pain threshold.[58]

Prostacyclins delivered via inhalation offer their own challenges and complications, including multiple treatments per day, as well as cough, which was the most commonly reported side effect noted in inhaled prostacyclin clinical trials. Persistent cough occurred in 54% of patients receiving active treatment with inhaled treprostinil and in 39% of patients receiving inhaled iloprost.[36,56]

### *Potential for Administration Errors*

Further complicating prostacyclin-based treatment, administration errors have been documented in association with use of these therapies, as evidenced by a study of 18 large PAH treatment centers in the United States conducted by Kingman and colleagues in 2010. Common causes of errors included accidental insertion of the wrong medication cassette at the time of administration (in 2 cases, epoprostenol was switched with treprostinil, resulting in a dosing error due to an infusion rate incompatible with the medication administered) and failure to start infusion pumps after replacing the cassette. Other errors included improper programming of the pump and errors in dosage calculations that could lead to possible administration of a prostacyclin bolus, resulting in hypotension and cardiopulmonary arrest requiring resuscitation.[57]

## Titration

Optimal dosing for patients receiving intravenous prostanoids, such as epoprostenol, remains highly variable among patients and among referral centers. Patients receiving too low a dose of prostacyclin therapy may experience suboptimal treatment effects, whereas patients receiving high-dose prostacyclins may experience intolerable side effects and/or deterioration due to high-output heart failure. Historically, prostacyclin doses were adjusted rapidly, resulting in side effects that led many patients to permanently abandon therapy.[30] In these early studies, doses were adjusted primarily based on changes in hemodynamic parameters and side effects, such as nausea, vomiting, severe headache, or anxiety.[53]

Today, prostacyclin dosages are titrated carefully over several weeks to months or more to find doses that yield the maximum benefit, balancing tolerability with PAH symptom improvement.[30] However, even when patients have been using prostacyclin infusions for a long period of time, retitration may be required. In some cases, a higher dose of medication may be necessary to attain the same effects previously achieved. This development of tolerance is known as tachyphylaxis. Although some investigators have interpreted this effect as a product of disease progression, pharmacologists have identified that reductions in IP receptor abundance and IP receptor sensitivity to prostacyclins with chronic therapy may be responsible for this effect. The substantial inter-individual variability in IP receptor expression may also be a factor in the highly individualized nature of prostacyclin dosing.[30,43]

## Role of Specialty Pharmacies

Because prostacyclin dose adjustment is a long-term process, specialty pharmacies are uniquely positioned to monitor the therapeutic regimen and offer evidence-based solutions to adjust therapy through collaboration with the healthcare team. On initiation of prostacyclin therapy, it is imperative that a clear treatment plan be communicated to all members of the healthcare team and that goals of the initial titration are fully understood.

### *Titration Management*

The specialty pharmacy plays an important role in the initial titration of the prostacyclin agents. Ideal orders

include precise intervals at which to make specific changes to the prostacyclin dose, a clear target dose, and enumeration of specific situations that would warrant prescriber engagement. Because the initial titration period often requires the patient to alter volumes of each ingredient in the mixing process, it is imperative that patients are provided with clear on-demand oral or written instructions by the dispensing pharmacist. Patients should be extensively counseled on expectations of therapy, should voice understanding of the mixing process, and must be empowered to report early any barrier to successful therapy.

Once a patient has achieved an initial maintenance dose, typically one with an optimal balance of minimal adverse events and improvement of symptoms of PAH, ongoing assessment by the specialty pharmacy helps patients maintain long-term prostacyclin treatment. This continual specialty pharmacy assessment process includes confirming prostacyclin dosing on every refill and inquiring about the presence of barriers to continuous successful therapy. Returning symptoms of PAH, adverse events associated with therapy, difficulties with admixture or medical equipment required to administer the product, and any early signs or symptoms of an infected central line are all examples of barriers to successful treatment that may be identified through the specialty pharmacy assessment.

The specialty pharmacy can also provide proactive clinical telephonic assessments by trained PAH nurses or pharmacists and continuous 24/7/365 access to a registered nurse or pharmacist, which enables patients to receive support in troubleshooting acute issues, facilitation of replacement delivery of supplies, and answers to questions regarding prostacyclin therapies. Because even temporary dose interruption of a continuously administered parenteral prostanoid can necessitate hospitalization, the availability of nurses and pharmacists may prevent emergency department visits and hospitalizations.

Through communication with the clinical prescriber, specialty pharmacy personnel enable prescribers to make more informed decisions regarding a long-term plan of care. Specialty pharmacy management of PAH therapies has been shown to improve adherence in patients with PAH, thereby improving disease state outcomes.[59]

## Addressing the Need for an Oral Agent

### *Underutilization*

Although prostanoids are well regarded as the gold standard of treatment for patients with severe forms of PAH,[30] prostanoid therapy is grossly underutilized, even in later stages of the disease. In the REVEAL registry, a substantial percentage of patients were not being treated with the recommended options of intravenous prostacyclin and/or combination therapy at time of death or after being assessed as worsening to FC IV. Only 43% of patients were receiving parenteral prostacyclin at the time of PAH-related death, and 8% of patients did not receive any PAH-specific therapy. Farber and colleagues postulated that some explanations for this underutilization include patients' or clinicians' unwillingness or inability to apply complex therapy or lack of belief in it as more efficacious than other drugs, as well as lack of acceptance, lack of referral to experienced PAH centers, and physician bias.[60]

### *Oral Treprostinil*

Traditional modes of administration, with their potential challenges and complications, may have contributed to an important unmet need: prostacyclin in an oral formulation. The first oral prostacyclin, sustained-release oral treprostinil (Orenitram), was approved for use in 2013. It is limited, however, by poor bioavailability (17%) and efficacy data based on a modest improvement in exercise capacity (6-minute walk distance [6MWD]).[6] Oral treprostinil was approved based on the results of 1 trial in which the drug was used as monotherapy.[61] It failed to show a benefit on the primary end point of exercise capacity improvement when used in combination with ERAs or PDE5 inhibitors in 2 combination trials (FREEDOM-C and FREEDOM-C2).[62,63] Oral treprostinil must be taken with food 2 to 3 times daily, with dosing based on clinical response.[6]

In pharmacokinetic studies, researchers identified substantially more peak-trough fluctuation with the twice-daily regimen versus the 3-times-daily regimen of oral treprostinil. With an oral treprostinil regimen administered 3 times daily, peak levels of treprostinil were 2.5 times higher than trough levels, whereas with twice-daily dosing, peak levels of treprostinil were 7 times higher than trough levels.[6,64] Clinical trials to date (FREEDOM-M, FREEDOM-C, and FREEDOM-C2) have not demonstrated a long-term benefit of oral treprostinil. The potentially long titration period and high rate of adverse events may deter some physicians and patients.[65]

### *Selexipag*

Selexipag, an orally bioavailable selective IP prostacyclin receptor agonist, was recently approved by the FDA. The structure of selexipag lacks the characteristic cyclo-

pentane ring of prostacyclin and its analogs.[1,33,36,66] Unlike existing prostacyclin therapies, selexipag and its active metabolite are very selective agonists of the prostacyclin receptor, also called the IP receptor, with very low binding affinity for other prostanoid receptors. In addition to these pharmacologic differences from existing prostacyclins, it is important to note that selexipag demonstrated no tendency for tachyphylaxis than traditional infused prostanoids in animal models.[66-68]

Selexipag was studied in the largest (1156 patients) long-term, event-driven, phase 3 randomized controlled trial conducted to date in patients with PAH. Results, first reported at the American College of Cardiology meeting in March 2015, showed a long-term benefit of selexipag therapy on the combined end point of morbidity and mortality. Eighty percent of all enrolled patients were on a baseline PAH-specific medication (ERA, PDE5 inhibitor, or ERA and PDE5 inhibitor).[69] Patients received treatment with oral selexipag titrated over 12 weeks to an individualized highest tolerated dose (up to 1600 mcg twice daily, with lower dosage levels of 200, 400, 600, 800, 1000, 1200, and 1400 mcg twice daily).[70] Over the course of the event-driven trial, 7.1% of patients taking placebo and 14.3% of patients taking selexipag discontinued treatment due to adverse events.[69-71]

Morbidity and mortality events comprising the primary end point included all-cause death; hospitalization for worsening of PAH; worsening of PAH necessitating lung transplant, balloon atrial septostomy, or initiation of chronic oxygen therapy or parenteral prostanoid therapy; or disease progression (ie, in FC II/III patients at baseline, a decrease from baseline 6MWD of ≥15% and worsening in FC; in FC III/IV patients at baseline, a decrease from baseline 6MWD of ≥15% and need for additional PAH-specific therapy).[70,72] After a mean follow-up of 76 weeks (selexipag) and 71 weeks (placebo), with selexipag there was a 40% reduction in the risk of experiencing an event of the composite primary end point versus placebo (HR, 0.60; 99% CI, 0.46-0.78), which was a highly statistically significant result ($P$ <.0001).[69] This primary composite end point included hospitalization, which is an important source of costs in the management of PAH.

## Implications for Managed Care

### *Cost Perspectives*

The REVEAL registry has documented a clear increase in hospitalization burden for patients with PAH.[73] A study of costs in patients with PH covered under Medicare Advantage and commercial insurance plans examined hospitalization costs from January 2007 through October 2011. A total of 4009 adult patients with PH or other chronic pulmonary heart disease with at least 1 claim for a PAH-specific therapy were identified. Costs of hospitalization were adjusted to 2011 dollars using the consumer price index. The initial hospitalization incurred an average cost of $39,576 (SD: $96,707) among commercial insurance members, with a mean length of stay (LOS) of 10.0 days (SD 14.8), while the initial hospitalization in patients with Medicare Advantage incurred an average cost of $16,496 (SD $31,301) over a mean LOS of 12.7 days (SD 21.0).[74]

After an initial hospitalization, subsequent hospitalizations tended to become longer and more expensive. Investigators analyzed data from a subset of 1203 patients in the main analysis who experienced at least 1 rehospitalization during the study period. Of these rehospitalizations, more than 1 in 5 (21.2%) occurred within 30 days after discharge from the initial hospitalization. Rehospitalizations occurring in the year after the initial hospitalization incurred an average cost of $35,188 (SD $152,006) among commercial insurance members and lasted a mean of 10.19 days (SD 23.33). Patients with Medicare Advantage incurred an average cost of $19,170 (SD $41,905) over a mean of 11.46 days (SD 18.73).[74]

In a retrospective observational cohort study of Medicare beneficiaries and commercially insured patients encompassing data from 15 million covered lives annually, researchers identified 12,306 patients taking PAH-specific medications, including prostacyclins. Costs on a per-patient basis accrued over 3 months before index prostacyclin therapy averaged $7598 (SD: $9950) for PAH-related medications and $24,222 (SD $63,295) for PAH-related medical care, totaling $31,819 (SD $63,280) for all PAH-related costs and $39,866 (SD $68,857) for all medical costs incurred.[75] These retrospective claims database research studies demonstrate the high healthcare resource utilization and costs for PH patients. Agents that decrease healthcare utilization (eg, hospitalization) may positively impact these expenditures.

### *Managed Care Role*

Managed care decision makers are charged with evaluating medications to determine the best values in treatment options. These decision makers must understand treatment advances, including those in rare diseases such as PAH. While prostacyclin therapies have been available for 2 decades,[1] these medications have largely been used in advanced disease and in a small fraction of PAH patients. In a recent retrospective study, Schneider and

colleagues found that prostacyclin prescribing remained relatively constant from 2010 to 2014, at about 21%. However, the distribution of scripts has changed, with an increase in nonparenteral prescriptions and a decrease in parenteral prescriptions.[76]

Recent treatment advances that target the prostacyclin pathway include a new oral prostanoid and a selective IP prostacyclin receptor agonist. These new oral agents may offer an opportunity for PAH patients to benefit from treatment of the prostacyclin pathway earlier in their disease process while avoiding some of the complications associated with traditional methods of administration. Decision makers must evaluate these 2 new oral agents for efficacy and cost-effectiveness, keeping in mind that only 1 of the agents has been studied in a long-term trial with a composite morbidity and mortality end point.[6,70]

Another consideration for managed care decision makers is the benefit under which these agents are paid. The inhaled and parenteral options have largely been reimbursed under the medical benefit, while oral formulations are generally covered under the pharmacy benefit. Integrated plans will experience a cost shift, with new costs accrued in the pharmacy benefit and a concomitant decrease in the medical spend. However, pharmacy-only coverage plans, such as Medicare prescription drug plans, will experience an increase in their overall drug spend due to a shift from the medical benefit, for which they have no financial responsibility. This additional drug spend may also decrease the medical spend through less healthcare resource utilization (such as hospitalizations).

### *Conclusion*

The prostacyclin pathway is the earliest pathway with treatment targets in PAH, with the first agent approved in 1995. Since that time, a number of agents, parenteral and nonparenteral, have been approved, but these routes of administration are fraught with challenges and complications. Inhaled agents are cumbersome and require frequent daily treatments. Parenteral agents, given subcutaneously or intravenously, offer challenges including potential BSIs, interruption of treatment through line breaks or blockages, considerable pain with subcutaneous infusion, considerable inconvenience and burden of 24-hour continuous infusions, and potential preparation and administration errors. An oral analog was approved in 2013, and a selective IP prostacyclin receptor agonist was approved in December 2015.

Prostacyclin therapies, regardless of the mode of delivery, require strong multidisciplinary collaboration among healthcare professionals, specialty pharmacies, and patients. The specialty pharmacy continues to play an important role in integration of care through distribution of medications and supplies, as well as patient education, advanced nursing services, and titration management of these medications.

As the treatment landscape for drugs that target the prostacyclin pathway expands from parenteral and inhaled therapies to oral treatments, many patients may benefit from exposure to these therapies at an earlier stage of their disease. Access to oral medications with long-term outcomes data, as well as the improved convenience of oral therapy, may help patients with PAH maximize function and maintain a more convenient and consistent therapeutic regimen to fight this devastating disease. This article has provided important information for decision makers as they evaluate new options and make formulary and coverage decisions for their patient populations.

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Notes

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