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M E D I C A L

# CROSSFIRE®

DEBATES, PEER EXCHANGE, AND INSIGHTS IN MEDICINE®

**SPECIAL EDITION**

## **Pulmonary Arterial Hypertension** Opportunities and Strategies for Medical Intervention

CME-Certified Activity

### PANELISTS

**David B. Badesch, MD**

University of Colorado Health Sciences Center  
Denver, Colorado

**Vallerie V. McLaughlin, MD**

University of Michigan Health System  
Ann Arbor, Michigan

**Richard N. Channick, MD**

UCSD Medical Center  
La Jolla, California

**Ronald J. Oudiz, MD**

David Geffen School of Medicine at UCLA  
Torrance, California

### MODERATOR

**Peter L. Salgo, MD**

National Television Medical Correspondent;  
Columbia University College of Physicians and Surgeons  
New York, New York

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1. a. Although PAH may be asymptomatic, the most common presenting symptom is dyspnea on exertion. Dyspnea is eventually present in all patients and in the later stages may be present even when the patient is at rest.

**Locator:** PAH: Recognition and Diagnosis

2. b. Dr. Channick explained that “there are groups of patients who are considered to be at significantly high risk in the normal population, and in whom we need to be especially vigilant.” These include patients who have underlying connective tissue disease (especially scleroderma), patients with liver disease, patients with a history of certain drug exposure (e.g., anorexiants, amphetamines, cocaine), patients who have underlying HIV, and patients with congenital heart disease. In patients with unexplained PAH, the guidelines recommend that testing for connective tissue diseases and HIV infection be performed.

**Locator:** PAH: Recognition and Diagnosis

3. d. In patients with suspected PAH, right-heart catheterization is required to confirm the presence of PAH, establish the specific diagnosis, and determine the severity of PAH.

**Locator:** PAH: Recognition and Diagnosis/Vasodilator Testing

4. a. Dr. McLaughlin described the primary purpose of acute vasodilator testing, “to identify the very small subpopulation that may have a good long-term response to oral calcium channel blocker therapy. This has been seen mostly in the population with idiopathic PAH.”

**Locator:** PAH: Recognition and Diagnosis/Vasodilator Testing

5. d. Dr. McLaughlin listed the three agents commonly used for vasodilator testing: intravenous epoprostenol, intravenous adenosine, and inhaled nitric oxide.

**Locator:** PAH: Recognition and Diagnosis/Vasodilator Testing

6. a. “IV epoprostenol is FDA approved for functional Class III and IV patients, and it is clearly the appropriate therapy for a critically ill patient,” declared Dr. McLaughlin, adding that, “for patients who are not as ill, but who have poor prognostic indicators, we consider epoprostenol as well.”

**Locator:** Receptor Targets for Therapy of PAH/Prostacyclin Pathway and Therapies/Intravenous Epoprostenol.

7. b. Sildenafil is a phosphodiesterase inhibitor that targets the nitrous oxide pathway by enhancing the effects of cyclic TNP, so that nitric oxide produced has a prolonged effect in the vasculature. This results in smooth muscle relaxation of the pulmonary vasculature. Sildenafil has recently been approved for the treatment of PAH, and has been shown to improve exercise capacity, WHO functional status, and hemodynamics in patients with Class II or III PAH.

**Locator:** Receptor Targets for Therapy of PAH/Nitric Oxide Pathway

8. d. Inhaled iloprost is a very-short-acting prostacyclin analog that can be delivered by nebulized inhalation. Trials of this agent as monotherapy have been performed in Europe and have suggested improvement in exercise tolerance and functional class. A trial performed in the US evaluated its use as add-on therapy to bosentan. “We tend not to use iloprost as initial monotherapy in our clinical practice, but we use it as add-on therapy for patients who are on oral therapy such as bosentan, yet are still symptomatic,” noted Dr. McLaughlin. She also explained that the majority of the clinical trial data of iloprost has been measured post-inhalation. “The improvements in exercise tolerance are more impressive post-inhalation than they are a few hours later,” she explained.

**Locator:** Receptor Targets for Therapy of PAH/Prostacyclin Pathway and Therapies/Inhaled Iloprost

9. c. Novel endothelin receptor antagonists selective for endothelin-A receptors, namely sitaxsentan and ambrisentan, are currently undergoing investigation in clinical trials.

**Locator:** Receptor Targets for Therapy of PAH/Endothelin Pathway/Endothelin Receptor Antagonists

10. b. “The conventional benchmark that has been used is the six-minute walk distance,” noted Dr. Oudiz. Non-invasive cardiopulmonary exercise testing such as the six-minute walk distance with gas exchange is a useful test, not only for early diagnosis of PAH, but also in the follow-up and evaluation of therapy. Indeed, the six-minute walk test has been the most widely-used measure of exercise capacity in PAH clinical trials.

**Locator:** Monitoring Treatment Response in Clinical Practice

# Pulmonary Arterial Hypertension

Opportunities and Strategies for Medical Intervention

CME-Certified Activity



Jointly Sponsored by the University of Medicine & Dentistry of New Jersey (UMDNJ)–Center for Continuing and Outreach Education and *Medical Crossfire*®/Liberty Communications Network.



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## Educational Overview

Pulmonary arterial hypertension (PAH) is a rare, progressive and debilitating lung disorder characterized by severe damage to the blood vessels of the lungs, which leads to progressive right ventricular failure and death. If left untreated, mortality is common within three years. Improving physician awareness and availability of non-invasive screening tools appears to have shortened the time to diagnosis. At the same time, advances are occurring in our understanding of the pathophysiology and potential management of this serious condition. Current and emerging medical strategies for PAH are targeting the prostacyclin, nitric oxide, and endothelin pathways.

Through debate and authoritative peer exchange, this *Medical Crossfire*® activity, conducted in conjunction with UMDNJ, will confront the opportunities and clinical challenges associated with the management of PAH.

## Target Audience

This educational activity is designed for pulmonologists and other health care professionals interested in or involved with managing patients with PAH.

## Learning Objectives

- Identify patients at risk for pulmonary arterial hypertension and describe an appropriate approach to diagnosis.
- List the main receptor targets for treatment strategies for pulmonary arterial hypertension.
- Design a therapeutic regimen based on overall risk:benefit considerations, including patient classification and prognostic factors.
- Discuss recent and emerging therapeutic options and how they may fit into the treatment algorithm for patients with PAH, including new agents and the role of add-on therapy.

## Method of Instruction

Participants should read the learning objectives and review the activity in its entirety. After reviewing the material, complete the self-assessment test consisting of a series of multiple-choice questions. The activity is complemented with references that contain the rationale for the correct answer to each question as well as a description identifying the section in the activity that contains the correct answer, allowing participants to review the material as needed, thus finalizing their educational participation.

Upon completing this activity as designed, participants will receive a letter of credit awarding AMA/PRA category 1 credit three to four weeks after receipt of the registration and evaluation materials. Estimated time to complete this activity as designed is one (1) hour.

## Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of UMDNJ–Center for Continuing and Outreach Education and *Medical Crossfire*®/Liberty Communications Network. UMDNJ–Center for Continuing and Outreach Education is accredited by the ACCME to provide continuing medical education for physicians.

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This activity was reviewed for relevance, accuracy of content, balance of presentation, and time required for participation by David J. Riley, MD; Sherene El-Sioufi, DO; and Jeffrey S. Kim, MD.

### **CME Academic Advisor**

David J. Riley, MD

Professor of Medicine

Pulmonary and Critical Care Division

University of Medicine & Dentistry of New Jersey—Robert Wood Johnson Medical School

New Brunswick, New Jersey

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**Dr. Badesch** has received grant/research support from Actelion, American Heart Association, American Lung Association, Boehringer Ingelheim Pharmaceuticals, CoTherix, Encysive Pharmaceuticals, Glaxo Wellcome/GlaxoSmithKline, ICOS/Texas Biotechnologies, Myogen, National Institutes of Health, Pfizer Labs, the Scleroderma Foundation, and United Therapeutics; and has served on the steering committees, advisory boards, and/or speakers' bureaus of Actelion, Astra-Merck, AstraZeneca Pharmaceuticals, Berlex Laboratories, Encysive Pharmaceuticals, Exhale Therapeutics/CoTherix, Forest Laboratories, Glaxo Wellcome/Glaxo-SmithKline, ICOS, Intermune, Mondo-Biotech, Myogen, Pfizer Labs, PR Pharmaceuticals, Scios, and United Therapeutics.

**Dr. Channick** has received grant/research support from Actelion, CoTherix, Lung Rx, Myogen, and Pfizer Labs; has been a consultant for Actelion and CoTherix; and has served on the speakers' bureaus of Actelion, CoTherix, and Pfizer Labs.

**Dr. McLaughlin** has received grant/research support from Actelion, CoTherix, Encysive Pharmaceuticals, Pfizer Labs, and United Therapeutics; has been a consultant for Actelion, CoTherix, Encysive Pharmaceuticals, Myogen, Pfizer Labs and United Therapeutics; and has served on the speakers' bureaus of Actelion, CoTherix, Pfizer Labs, and United Therapeutics.

**Dr. Oudiz** has received grant/research support from Actelion, CoTherix, Encysive Pharmaceuticals, Lilly-ICOS, Myogen, Pfizer Labs, and United Therapeutics; has been a consultant for Actelion, CoTherix, Encysive Pharmaceuticals, GlaxoSmithKline Pharmaceuticals, Myogen, and Pfizer Labs, and has been a member of the scientific advisory boards of CoTherix and Myogen.

**Dr. Salgo** has no financial arrangements or affiliations to disclose.

**Dr. Riley, Dr. El-Sioufi, and Dr. Kim** have no financial arrangements or affiliations to disclose.

### **Off-Label Usage Disclosure**

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# Pulmonary Arterial Hypertension

## Opportunities and Strategies for Medical Intervention

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### PANELISTS

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**David B. Badesch, MD**

Professor of Medicine  
Divisions of Pulmonary Sciences & Critical Care Medicine  
Clinical Director, Pulmonary Hypertension Center  
University of Colorado Health Sciences Center  
Denver, Colorado



**Vallerie V. McLaughlin, MD**

Associate Professor of Medicine  
Director, Pulmonary Hypertension Program  
University of Michigan Health System  
Ann Arbor, Michigan



**Richard N. Channick, MD**

Associate Clinical Professor of Medicine  
Division of Pulmonary and Critical Care Medicine  
UCSD Medical Center  
La Jolla, California



**Ronald J. Oudiz, MD**

Associate Professor of Medicine  
David Geffen School of Medicine at UCLA  
Director, Liu Center for Pulmonary Hypertension  
Los Angeles Biomedical Research Institute  
at Harbor-UCLA Medical Center  
Torrance, California

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### MODERATOR

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**Peter L. Salgo, MD**

National Television Medical Correspondent;  
Clinical Professor of Medicine and Anesthesiology  
Columbia University College of Physicians and Surgeons  
New York, New York

**P**ulmonary arterial hypertension (PAH) is a relatively rare progressive disorder characterized by high blood pressure in the lungs. The condition leads to eventual right-sided heart failure and an inability to pump blood through the pulmonary artery to the lungs. PAH affects people of all ages and ethnic backgrounds in the US, and is without a known cure. At the same time, PAH is an area that has seen major progress during the past five to 10 years, largely due to a number of controlled clinical trials. Thus, it has moved from an essentially untreatable disease to one with multiple options for therapy. To explore these and other issues, **Medical Crossfire** convened a panel of national experts to offer their insights.

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### **PAH: Recognition and Diagnosis**

To begin this *Medical Crossfire*, moderator Peter L. Salgo, MD, asked the panel to define PAH and discuss issues associated with diagnosis of the condition.

Richard N. Channick, MD, began by stating that “Likely, the most widely-accepted definition of PAH is a pressure definition, which has been based on consensus over the years.” This hemodynamic definition, developed by the National Institutes of Health Registry on Primary Pulmonary Hypertension, has been adopted by the ACCP evidence-based clinical practice guidelines and has been widely used in clinical trials.<sup>1</sup> Using these criteria, PAH is defined by a mean pulmonary artery pressure  $\geq 25$  mm Hg, with a pulmonary capillary wedge pressure  $<15$  mm Hg; both measured at rest by right-heart catheterization. “A clinical definition of PAH might include such classic cardiac findings as a loud pulmonic component of the second heart sound and a murmur of tricuspid regurgitation,” Dr. Channick remarked, “but the pressure definition is the one that should be applied in practice.”

As the condition advances, the patient experiences shortness of breath at rest and is extremely limited in activities of daily life. Other symptoms such as chest pain, dizziness, and syncope may also occur. Although these symptoms may indicate PAH, they are

still non-specific, making it important to rule out other possible causes for shortness of breath. Some patients can have mild PAH without large elevations in pulmonary arterial pressure, and physical findings may be absent in these patients. Although PAH may be asymptomatic, the most common presenting symptom is dyspnea on exertion. Dyspnea is eventually present in all patients and in the later stages may be present even when the patient is at rest.<sup>2</sup> However, even in its later stages, signs of the disease can be confused with other conditions that affect the heart and lungs.

Although the diagnosis of PAH is not straightforward, it remains the key to appropriate therapy.<sup>3</sup> Development of unexplained dyspnea on exertion and presyncope in the absence of abnormal pulmonary function test and abnormal chest radiograph should suggest the possible presence of PAH and precipitate an appropriate evaluation. Commenting on the diagnostic process, Dr. Channick stated that “The entire diagnostic approach begins with having a suspicion for the presence of PAH. Clinicians need to consider this diagnosis in a patient who comes in with shortness of breath or unexplained exercise intolerance.”

PAH may occur as an idiopathic process or as a result of other disease processes.<sup>2</sup> Dr. Channick explained that “there are groups of

patients who are considered at significantly higher risk, and in whom we need to be especially vigilant.” These include patients who have underlying connective tissue disease (especially limited scleroderma), patients with liver disease, patients with a history of certain drug exposure (e.g., anorexiants, amphetamines, cocaine), patients who have underlying HIV, and patients with congenital heart disease. In patients with unexplained PAH, the guidelines recommend that testing for connective tissue diseases and HIV infection be performed.<sup>1</sup>

“Early diagnosis of PAH by physicians, in general, has improved during the last decade,” noted David B. Badesch, MD. “In the early 1990’s, we frequently did not see patients in referral centers until they were very ill. In those cases, the hemodynamic findings were more severe, and the echocardiographic findings of right heart failure were often present. Patients presented almost exclusively in functional classes III and IV at that time.” He added that due to previous and ongoing educational efforts, “awareness of PAH among practicing pulmonologists, internists, and cardiologists has improved and the disease is beginning to be recognized more promptly.”

In summary, Ronald J. Oudiz, MD, concluded by stating that, “it is important for physicians first to understand that a clinical suspicion for PAH must be present, since it is a relatively rare disorder. Second, a thorough workup must follow in order to be sure that the more common causes of pulmonary hypertension are excluded. And third, the workup must include cardiac catheterization.”

### *Echocardiography*

In patients with a clinical suspicion of PAH, Doppler echocardiography may be performed as a noninvasive screening test to detect PAH. “What should clinicians look for with this diagnostic test?” asked Dr. Salgo.

Vallerie V. McLaughlin, MD, began by noting that “In a patient who has exertional dyspnea without another clear explanation

such as left heart disease or pulmonary dysfunction, one would likely start with an echocardiogram to decide whether to engage in the full diagnostic algorithm for PAH. The echocardiogram can estimate pulmonary artery pressures using the tricuspid valve regurgitation velocity. We also look for enlargement of the right atrium and right ventricle, and dysfunction of the right ventricle.”

Dr. McLaughlin added that “in advanced PAH, because the right ventricle becomes so large and because the resistance through the pulmonary vasculature is so high, the left ventricle does not fill. Sometimes, you see a very small underfilled left ventricle and septal flattening.” Doppler echocardiography may, however, be imprecise in determining actual pressures compared to invasive evaluation, she concluded.

Offering his perspective, Dr. Oudiz asserted that “Dr. McLaughlin points out an important caveat regarding echocardiography and PAH. It is not a substitute for cardiac catheterization, and acting on the echo findings alone may put the patient at unnecessary risk.”

An additional issue, he noted, relates to the diagnostic use of exercise echocardiography in patients with symptoms and apparently normal resting PA pressure. “This particular modality may also be inaccurate and cannot accurately estimate left ventricular filling pressure with exercise. Again, acting empirically on the findings of an exercise echocardiogram may invite trouble.”

### *Vasodilator Testing*

Dr. Salgo then asked the panel to discuss the role of acute vasodilator testing.

Dr. McLaughlin described the primary purpose of acute vasodilator testing, “to identify the very small subpopulation that may have a good long-term response to oral calcium channel blocker therapy. This has been seen mostly in the population with idiopathic PAH.”

Dr. Badesch went on to clarify that “A patient who responds to vasodilator testing in the catheterization lab and then subse-

quently responds to calcium channel blocker therapy tends to have a significantly better prognosis.” He referred to a study by Rich and colleagues that showed improved survival in vasoreactive patients treated with calcium channel blockers.<sup>4</sup> Because of this, testing of vasoreactivity is an important part of the initial patient assessment.<sup>3</sup>

Dr. McLaughlin then explained the process of vasodilator testing. “After obtaining the baseline set of hemodynamic measures at the time of cardiac catheterization, one then administers one of the vasodilators and remeasures the hemodynamic parameters, including the pulmonary artery pressure and the cardiac output,” she explained. Although the precise definition of a favorable response is still being debated, response may be defined by a reduction in the mean pulmonary artery pressure by at least 10 mm Hg to an absolute mean pulmonary pressure of less than 40 mm Hg in the setting of an unchanged or an increased cardiac output.<sup>3</sup>

Due to the potential dangers inherent in vasodilator testing, it is recommended that this test be conducted by experienced professionals in a referral center.<sup>3</sup> Dr. McLaughlin pointed out that three agents are commonly used for vasodilator testing: intravenous epoprostenol, intravenous adenosine, and inhaled nitric oxide.<sup>3</sup> “Each center likely has a ‘favorite’ agent to use,” she suggested. “At the University of Michigan, we use inhaled nitric oxide because we find it to be safe, quick, and a very good prognostic indicator of determining channel blocker response.”

“Unfortunately, we are learning over time that the true proportion of vasoresponders is actually a relatively small percentage of patients,” lamented Dr. Badesch. “The definition of true vasoreactivity has become more stringent over time, and the number of true responders appears to be lower than was previously appreciated,” he explained, noting that the percentage is currently believed to be approximately 10% of all patients referred to pulmonary vascular units.<sup>5</sup> “Those individuals who are truly vasoreactive tend to do

well over a period of years on calcium channel antagonists.” He concluded by pointing out that, “occasionally, these patients will lose their responsiveness to those medications and will need to be treated with other agents.”

Commenting on the use of calcium-channel blockers, Dr. Channick cautioned that, “these agents should not be used empirically to treat PAH in the absence of demonstrated acute vasoreactivity.” He pointed out that “these drugs have been overused in PAH because they are easy to prescribe and physicians are comfortable with them. But they likely cause a fair amount of harm for the simple reason that very few patients benefit from calcium channel blockers long term. It really is a very strong message: never prescribe a calcium blocker to a patient with pulmonary arterial hypertension unless you really can determine that the patient is in the rare, highly vasoreactive group.”

“It is important to understand that, regardless of response to vasodilator testing, the use of calcium channel antagonists is contraindicated when the right atrial pressure is elevated and the cardiac output is reduced,” added Dr. Oudiz. “Both findings are signs of advanced right ventricular failure, which places the patient at high risk for developing acute decompensation when calcium antagonists are used.”

### *Prognostic Indicators*

Moving on to discuss other prognostic indicators, Dr. Badesch explained that “In terms of determining the prognosis of other patients based on hemodynamic testing alone, we learned from an NIH-sponsored registry in the 1980s that low cardiac output and high right atrial pressure are likely predictors of a poorer prognosis.” He offered that at the time the registry was conducted, it was thought that perhaps a higher pulmonary artery pressure predicted a poorer prognosis, but this view is now being questioned. “We know that if the patient becomes more pro-

gressively ill, the pulmonary artery pressure can fall off over time due to worsening right ventricular function,” he posited. Other factors that have been shown to predict poor outcome include Class IV status and baseline six-minute walk distance.<sup>6,7</sup>

Dr. Oudiz noted that a number of prognostic markers have been studied in retrospective analyses of PAH patients. “These include functional class and six-minute walk testing, as Dr. Badesch points out. And additional measures such as eccentricity index by echocardiogram, presence of pericardial effusion, troponin T elevation, uric acid levels, and peak oxygen consumption have also been shown to be prognostic. In clinical practice, a synthesis of all available data are used to determine disease severity,” he concluded.

## Receptor Targets for Therapy of PAH

Currently, multiple major pathways are known to be involved in the abnormal proliferation and contraction of smooth muscle cells in the pulmonary arteries of patients with PAH.<sup>3</sup> There has been a focus on targeting three of these pathways for improving outcomes in PAH. According to Dr. McLaughlin, “These pathways—prostacyclin, nitric oxide, and endothelin pathways—are important because those are where we have targeted therapies for PAH.” Dysfunctional pulmonary artery endothelial cells have diminished production of prostacyclin and nitric oxide synthase in addition to increased production of endothelin-1. This scenario contributes to vasoconstriction and proliferation of smooth muscle cells in the pulmonary arteries. Current and emerging therapies modulate these specific targets in smooth muscle cells in the pulmonary arteries. In addition to their actions on smooth muscle cells, prostacyclin analogues and nitric oxide have other actions, including antiplatelet effects, which may account for their clinical efficacy in patients with PAH.

## Prostacyclin Pathway and Therapies

Prostacyclin, a metabolite of arachadonic acid produced primarily in the vascular endothelium, is a potent vasodilator that affects both the systemic and pulmonary vasculatures. A relative deficiency of prostacyclin may contribute to the pathology of PAH.<sup>3</sup> Thus, it is not surprising that prostacyclin analogues have been explored for the treatment of PAH and have been found to confer beneficial effects. Many of the agents that are approved for PAH have indications based on the New York Heart Association/World Health Organization Classification of Functional Status of Patients with PAH; **Table 1** provides a summary of each functional class.<sup>8</sup>

The therapies outlined in the current *American College of Chest Physicians Guidelines* include bosentan, treprostinil, eprostenol, and iloprost.<sup>3</sup> “Sildenafil was under investigation at the time that the last guidelines were issued, but has since been approved,” noted Dr. Badesch. The guidelines will be revised based on evidence that has become available since the original version was published. “Important studies have been released in the interim, which will also be taken into consideration,” he added.

**Intravenous Epoprostenol.** Epoprostenol has a half-life of approximately five minutes and is given via continuous intravenous (IV) administration via a permanent indwelling central venous catheter, using a small battery-powered pump for continuous infusion. IV epoprostenol has been used for the treatment of PAH since the 1980’s. “IV epoprostenol is FDA approved for functional Class III and IV patients, and it is clearly the appropriate therapy for a critically ill patient,” declared Dr. McLaughlin, adding that “For patients who are not as ill, but who have poor prognostic indicators, we consider epoprostenol as well. For example, if a patient is in functional Class III, but has a very high right atrial pressure, low cardiac output, or a low six-minute walk distance, sometimes we do go directly to epoprostenol. Obviously, this

regimen is much more complicated for the patient than an oral therapy. Still, this is a very potent agent and is likely the fastest in onset for stabilization.”

Dr. Oudiz maintained that, “a major factor in considering PAH therapy today is the experience and volume of data accumulated on a particular drug. Epoprostenol has been around the longest, and is generally accepted as perhaps the most potent PAH therapy available and regarded by many as a gold-standard treatment by which others are compared.”

Offering his perspective on this issue, Dr. Channick stated, “Given the availability

of several medications including oral and inhaled therapies—and the ability to combine these therapies—the number of patients needing epoprostenol is clearly decreasing,” and added that, “We do, however, need more data on the comparable efficacy of these regimens to epoprostenol.”

**Subcutaneous treprostinil.** The potential complications related to the need for central venous administration of epoprostenol have led to the development of other prostacyclin analogs delivered by other routes of administration. Treprostinil is structurally very similar to epoprostenol, but is stable at room temperature and has a longer half-life. It can therefore be given subcutaneously. Novel prostanoids such as subcutaneous treprostinil have beneficial effects in many patients, although there are no long-term data on survival benefits.

Dr. McLaughlin summarized the current evidence on these agents by stating that, “The clinical trials with treprostinil have demonstrated improvement in exercise tolerance; this benefit was more modest than what we have seen in clinical trials of epoprostenol, which may reflect that higher doses of treprostinil are sometimes needed.” Simonneau and colleagues demonstrated modest but significant improvements in six-minute walk tests with continuous subcutaneous infusions of treprostinil compared to placebo, which were more impressive in patients who could tolerate the highest doses.<sup>9</sup>

The main drawback of subcutaneous treprostinil, Dr. McLaughlin noted, is that a majority of patients experience pain and erythema at the site of the subcutaneous infusion. “It takes a very dedicated nurse to help that patient work through some of the local site reactions. If a patient can tolerate the local site reactions, then subcutaneous treprostinil can be used very effectively.”

Dr. Oudiz cited agreement with his colleague, “The key issue with the data on treprostinil is that of infusion site pain, which may have limited dose-escalation in

TABLE 1

**World Health Organization Classification of Functional Status of Patients with PAH**

Class	Description
I	Patients with PAH 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 PAH 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 PAH 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 PAH who are unable to perform any physical activity at rest 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.

the clinical trials. Clearly, the clinical response to adequate doses of treprostinil has been very favorable.”

**Inhaled Iloprost.** Inhaled iloprost is a short-acting prostacyclin analog that can be delivered by nebulized inhalation. Trials of this agent as monotherapy have been performed in Europe and have suggested improvement in exercise tolerance and functional class.<sup>10</sup> A trial performed in the US called the STEP study evaluated its use as add-on therapy to bosentan.<sup>11</sup> “We tend not to use iloprost as initial monotherapy in our clinical practice, but we use it as add-on therapy for patients who are on oral therapy such as bosentan, yet are still symptomatic,” noted Dr. McLaughlin.

“If inhaled iloprost has such a short half-life, is it only effective during its half-life?” asked Dr. Salgo.

“That is an excellent question,” responded Dr. McLaughlin, pointing out that the majority of the clinical trial data has been measured post-inhalation. “The improvements in exercise tolerance are more impressive post-inhalation than they are a few hours later,” she explained. As a result of this, inhaled iloprost needs to be administered up to six to nine times per day.

Dr. Channick added that, “We actually do not know whether this frequency of inhalation is necessary in patients on concomitant oral therapy. The efficacy of iloprost does appear to last beyond its half-life.”

**Beraprost.** Beraprost is an oral prostacyclin analog that showed an improvement in six-minute walk distance in a European trial,<sup>12</sup> but which did not demonstrate sustained improvement in exercise tolerance in a later US trial.<sup>13</sup> Dr. McLaughlin noted that “This drug is not available in the US, and it likely will not be.” On the other hand, she said, “there is an oral analog of treprostinil that has a longer half-life, which will be the subject of clinical trials in the coming year.”

**Comparing Prostacyclins.** Dr. Salgo asked the panel if “there are differences in the

comparative efficacies of the prostacyclins dependent upon their route of administration.”

Acknowledging that a comparative clinical trial would provide a definitive answer but that one is not available, Dr. McLaughlin stated that, given her personal experience, “I consider epoprostenol the ‘gold’ standard. When it is given in adequate doses, treprostinil may be as effective.” In her practice, she has found inhaled iloprost “to be not quite as effective as epoprostenol when used as monotherapy. However, there may be a role for it in combination therapy with an oral agent for patients who need more, but are not willing or not ill enough to go on an intravenous form of therapy.”

The downside of continuous intravenous therapy with epoprostenol, she continued, “is that there is no doubt that it changes a patient’s life, with the potential for infusion-site infections, or the need for an emergency department visit if their Hickman catheter is accidentally disconnected. It affects the patients immensely. This is one of the reasons why most patients would prefer to start with an oral therapy if it is right for them.” She added that there is also the potential for “very serious complications of being off the drug for even short periods of time, so vigilance is required.” The upside of epoprostenol is that its use in severely ill patients clearly prolongs survival.<sup>5</sup>

Offering an alternate perspective on the prostacyclins, Dr. Oudiz remarked, “I have not been convinced that treprostinil is less potent. Also, we have seen dramatic clinical responses with all classes of drugs. So I believe that, in individual patients, one class or one particular drug within a class might be more effective than another and we do not yet know how to predict that response. However, I agree with Dr. McLaughlin that epoprostenol remains as the current gold standard in our armamentarium.”

### *Nitric Oxide Pathway*

Dr. Salgo next asked the panel to address the use of nitric oxide.

Dr. Oudiz explained that “Nitric oxide is an endogenous substance that is naturally occurring in the body, and in patients with PAH, nitric oxide production is reduced. It stands to reason that, like epoprostenol, if the nitric oxide level is a marker of disease severity as well as a modulator of the disease process, then giving exogenous nitric oxide may have a beneficial effect.” One potential issue is that nitrous oxide itself has such a short half-life that it must be administered via continuous inhalation.

Sildenafil is a phosphodiesterase inhibitor that targets the nitric oxide pathway by enhancing the effects of cyclic GNP within the pulmonary vasculature, so that the effects of nitric oxide are prolonged in the vasculature. This results in smooth muscle relaxation of the pulmonary vasculature. Sildenafil has recently been approved for the treatment of PAH. In a recent study, 278 patients with symptomatic PAH were randomized to placebo or sildenafil (20, 40, or 80 mg) orally three times daily for 12 weeks. The main outcome measure was the change from baseline to week 12 in the distance walked in six minutes. In all sildenafil groups, the distance walked in six minutes increased from baseline. The mean placebo-corrected treatment effects were 45 meters, 46 meters, and 50 meters for 20, 40, and 80 mg of sildenafil, respectively. All sildenafil doses were associated with lower mean pulmonary-artery pressure, and improved WHO functional class. The incidence of clinical worsening did not differ significantly between the sildenafil groups and the placebo group. Adverse effects reported in the trial included flushing, dyspepsia, and diarrhea.<sup>14</sup>

### *Endothelin Pathway*

Endothelin receptor antagonism has emerged as an important therapeutic target for the treatment of patients with PAH. Endothelin-1 is overexpressed in several forms of pulmonary vascular disease, contributing to the development and/or progression of pulmonary vasculopathy.<sup>15</sup> According to Dr.

Oudiz, “Recent investigations have suggested that endothelial dysfunction may be one of the mediators, if not instigators, of disease process in the pulmonary vasculature in patients with PAH.”

There are at least two types of endothelin receptors: endothelin-A receptors which are vasoconstrictive, and endothelin-B receptors which are vasodilatory and may also be involved in the clearance of endothelin. Endothelin receptor antagonists can dilate the pulmonary artery system.

**Endothelin Receptor Antagonists.** As a class, it appears that endothelin receptor antagonism is associated with improved exercise capacity and some measures of hemodynamics in symptomatic patients with PAH.<sup>16</sup> Bosentan is the first orally-active endothelin receptor antagonist approved by the FDA for Class III and IV patients with PAH. A recent study has reported the long-term results of two trials of patients with severe PAH treated with bosentan, and showed that first-line therapy with the endothelin antagonist bosentan was associated with improved survival compared to a predicted formula derived from the NIH PAH registry.<sup>7</sup> Hepatotoxicity is a real concern with the use of bosentan, occurring in about 8% to 10% of PAH patients taking bosentan, and requires close monitoring of the patient. In addition, there is a risk of teratogenicity.<sup>3</sup>

Novel endothelin receptor antagonists selective for endothelin-A receptors, namely sitaxsentan and ambrisentan, are undergoing investigation in clinical trials. Sitaxsentan was the first selective endothelin receptor antagonist to be evaluated for the treatment of patients with PAH in a placebo-controlled multicenter study.<sup>17</sup> Both the 100 mg and 300 mg doses that were studied resulted in improvements in six-minute walk distance, functional class, cardiac index, and pulmonary vascular resistance compared with placebo. However, the 300 mg dose was associated with unacceptable hepatotoxicity rates. The STRIDE-1 study also showed improvements in the subpopulations usually

included in clinical trials (i.e., Class III and IV patients) treated with sitaxsentan.<sup>18</sup>

Ambrisentan is an investigational drug being developed as once-daily oral therapy for patients with PAH. It has orphan drug status for the treatment of PAH in the US and European Union. Dose-finding studies of ambrisentan showed the ability to improve exercise capacity, symptoms, and hemodynamics in patients with PAH.<sup>19</sup> The incidence and severity of liver enzyme abnormalities appear to be very low. Results of the ARIES-2 trial, one of two Phase 3 clinical trials of ambrisentan, have recently been disclosed and are pending formal presentation and publication. ARIES-2 was a double-blind, placebo-controlled trial that evaluated once-daily oral doses of 2.5 mg and 5 mg of ambrisentan. The primary efficacy endpoint was exercise capacity, measured as the mean change from baseline at 12 weeks in the six-minute walk distance, compared to placebo. These results suggest that improvement in exercise capacity with ambrisentan is significant and that the onset of effect occurs rapidly. Time to clinical worsening was also delayed.<sup>20</sup> None of the patients taking ambrisentan in this trial developed hepatotoxicity.

“There are studies with both ambrisentan and sitaxsentan that are pending publication at this time,” noted Dr. Badesch. Further investigation will determine what potential role selective endothelin receptor antagonists will play in the treatment of PAH.

“Whether or not they will be superior to the currently-approved bosentan in terms of efficacy and/or safety is not entirely clear yet,” offered Dr. Channick. “Assuming they receive approval, we will certainly need more experience with these drugs over time to make that determination.”

“As our understanding of the pathophysiology of the disease expands over the ensuing years, it should allow us to develop other targeted treatments in addition to treatment that targets the three pathways we have discussed,” forecast Dr. McLaughlin.

“There is a structural component to the disease that appears to include a prolifera-

tion of endothelial cells,” added Dr. Badesch. “Addressing that structural or proliferative component of the disease is going to be the focus of some newer forms of therapy.”

Offering his perspective, Dr. Oudiz remarked that “there likely is not any one pathway that we will be able to target alone and effectively reverse the disease. We need to develop a multifaceted approach.”

### *Role of Combination Therapy*

Due to the complexity of PAH, as Dr. Oudiz noted, targeting a single pathway might not maximize the potential benefits of therapy. Combining agents with different modes of action has been suggested as a strategy that may improve symptoms, hemodynamics, and long-term outcome. Seeking insight into the use of combination therapy, Dr. Salgo asked the panel to comment on its role in clinical practice.

“The concept of starting multiple drugs up-front is one with strong rationale,” asserted Dr. Channick. He explained that there are two approaches to combination therapy: up-front combination therapy or add-on therapy. “As we discussed, there are multiple abnormalities in the endothelium associated with this disorder, and it certainly would make sense logically to target more than one receptor.”

Dr. Channick lamented the fact that currently, there are limited data on combination therapy strategies. “For practical reasons, most of the available studies have evaluated add-on therapy,” he remarked.

“In the STEP study,<sup>11</sup> the addition of inhaled iloprost in patients still symptomatic on bosentan appeared safe and resulted in improvements in six-minute walk distance, hemodynamics, and time to clinical worsening,” offered Dr. McLaughlin.

Dr. Channick added that “My experience has been fairly consistent that when another drug is added to monotherapy, further clinical benefit can be achieved. The concept of multiple drugs up-front may in fact be the best approach—but we do not have definitive data to support this yet.”

“Exchanging information from anecdotal experiences and from small investigator-initiated trials is one way we learn about possible therapeutic strategies that can pave the way for clinical trials,” added Dr. Oudiz. “This information is often part of the framework upon which new trials are designed.”

“There are a number of clinical trials that are ongoing, as well as trials scheduled to begin in the next year or so, that will study the concept of combination therapy,” Dr. McLaughlin pointed out. “If we work together, we can hopefully answer some of these questions in a controlled, evidence-based fashion.”

Commenting on the use of up-front combination therapy, Dr. Oudiz stated, “I see the future of PAH therapy as one that might mimic that of congestive heart failure. That is, an approach in which several receptors are targeted up-front, with evidence-based rationale for individual therapies and for the combinations, resulting in incremental clinical benefits above that of monotherapy.”

### **Monitoring Treatment Response in Clinical Practice**

“Whatever agents a physician chooses to use, response to treatment needs to be monitored in clinical practice,” noted Dr. Salgo. “How do you go about following these patients?”

“The conventional benchmark has been the six-minute walk distance,” responded Dr. Oudiz. Indeed, the six-minute walk test has been the most widely-used measure of exercise capacity in PAH clinical trials.<sup>21</sup> Non-invasive cardiopulmonary exercise testing with gas exchange is a useful test, not only for early diagnosis of PAH, but also in the follow-up and evaluation of therapy. Dr. Oudiz went on to convey that “At Harbor, we rely a great deal on cardiopulmonary exercise testing because it describes the pathophysiologic abnormalities of PAH. More importantly, it shows us what I call the ‘fingerprint’ of the PAH disease process, ventilatory inefficiency.” This is an indirect measure of how well the lungs are perfused during exercise, which

is when most patients are symptomatic.

“Symptoms also are important to measure,” added Dr. McLaughlin. “There are data to suggest that if you can improve patients to functional Class I or II on therapy, they do better in the long term.” This has been demonstrated with IV epoprostenol, where patients who had enough improvement to warrant reclassification to Class I or II after epoprostenol therapy had a survival advantage.<sup>6,22</sup>

Dr. McLaughlin went on to agree that “The six-minute walk test is also an important, noninvasive way to assess the patient’s response to therapy. I tend to use echocardiography less often—I do not think it is the best way to describe right ventricular function. I perform periodic right heart catheterizations on patients, generally after the first year of therapy unless the patient is not doing well, in which case I may do it sooner to assess their hemodynamic response.” She also looks for reductions in the pulmonary pressure, “although with most of the therapies that we have discussed, normalization of the pulmonary artery pressure is not possible. Cardiac output is another parameter that is important to improve. If the patient is on a prostacyclin such as epoprostenol or treprostinil and their cardiac output is still low, I will try to increase the dose of that agent to optimize their hemodynamic response.”

Dr. Badesch offered that his institution “uses a combination of the outcomes that my colleagues have discussed.” He contended that “The six-minute walk test is a very useful functional assessment, which is used serially over time. I follow the results in a similar manner to what is done in clinical trials. The patient’s history is also of great importance—how are they feeling, how do they go about their day-to-day activities? Those measures are very useful in following patients, and those same sorts of assessments play into functional class assessment.”

Dr. Oudiz concluded by explaining that his institution utilizes serial echocardiography to noninvasively assess right ventricular pressure and function, as well as regular

catheterization on an as-needed basis, “especially when we are considering an alteration in therapy due to a change in clinical status or when we are considering transplantation.”

## Cost of Medical Therapy versus Transplantation

Shifting the discussion towards issues associated with the cost of therapies discussed in this *Medical Crossfire*, Dr. McLaughlin confirmed that “all of the treatment agents are quite expensive.” Costs can range from approximately \$11,000 to \$12,000 per year for oral sildenafil to approximately \$35,000 to \$40,000 per year for bosentan. The costs of therapy increase substantially when oral agents do not provide adequate treatment. IV epoprostenol, at the dosages most commonly used at referral centers, can cost between \$60,000 and \$100,000 per year, and higher. Inhaled iloprost can cost up to \$90,000 per year.

The counterargument to the high cost of medical therapy, noted Dr. Salgo, “is that the disease itself is expensive in terms of days lost from work, quality of life and survival.” He asked the panel, “Is there a balance point with these agents, compared to the benefit they offer?”

“That is a good point,” responded Dr. Channick. “We tend to focus on the dollar amount of the medication. It is more complicated than that. Certainly, if medications reduce the need for hospitalization or the need for lung transplantation, there should be cost savings.”

Dr. Badesch noted that “the up-front costs of lung transplantation could be \$150,000 to \$175,000, and the annual follow-up costs might be as much as \$15,000 to \$20,000 a year or more.”

“And that does not take into account the cost of all anti-rejection medications,” interjected Dr. McLaughlin.

Dr. Badesch acknowledged that “although we do not have a great deal of information,

our general feeling is that effective medical therapies may actually save money in terms of hospitalization and need for transplantation. Anecdotally, we are doing fewer lung transplants in PAH patients than we were before these medications became available.” He continued, “Early on we viewed transplantation as being necessary in many of our patients. But in the past decade, it has been realized that medical therapy can significantly delay transplantation.”

## Final Thoughts

In offering his take-away message for this *Medical Crossfire*, Dr. Channick summarized the advances that have occurred and the available opportunities for pulmonologists. “PAH is no longer a universally fatal disease. Effective therapy is available, and I urge pulmonologists and cardiologists to have a high index of suspicion for PAH,” adding that “appropriate referral and diagnostic work-up are critical first steps.”

Dr. Badesch lauded educational efforts, which have played an important role in increasing awareness of the disease and encouraging referral to centers of excellence. “Most patients should receive care in referral centers or centers of excellence,” he remarked.

Dr. McLaughlin agreed with the need for judicious application of drug therapy. “One point that I would emphasize is that the indiscriminate use of calcium channel blockers is ill-advised. The patients who will respond are few and far between. There are other options available for patients who do not respond to acute vasodilators.”

To conclude this *Medical Crossfire*, Dr. Oudiz summarized the current medical status of PAH. “This decade has already seen quite a bit of advancement in the area of PAH. There is better awareness, earlier diagnosis, and the availability of better treatment, and it is only getting better.” Closing on an optimistic note, Dr. Oudiz posited that “As time goes on, we will have access to new therapies that are going to be safer and more efficacious.” ■

## REFERENCES

- Rubin LJ. Diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*. 2004;126:4S-6S.
- McGoon M, Guterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*. 2004;126:14-34.
- Badesch DB, Ahman SH, Ahearn GS, et al. Medical therapy for pulmonary arterial hypertension. ACCP evidence-based clinical practice guidelines. *Chest*. 2004;126:35S-62S.
- Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med*. 1992;327:76-81.
- Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med*. 2004;351:1425-1436.
- Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol*. 2002;40:780-788.
- McLaughlin VV, Sitbon O, Badesch DB, et al. Survival with first-line bosentan in patients with primary pulmonary hypertension. *Eur Respir J*. 2005;25:244-249.
- Rich S. Primary pulmonary hypertension: executive summary. Evian, France: World Health Organization, 1998.
- Simonneau G, Barst RJ, Galiè N, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind randomized controlled trial. *Am J Respir Crit Care Med* 2002;165:800-804.
- Olschewski H, Simonneau G, Galiè N, et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med*. 2002; 347:322-329.
- McLaughlin VV, Sitbon O, Badesch DB, et al. A randomized, double-blind, placebo-controlled study of iloprost inhalation as add-on therapy to bosentan in pulmonary arterial hypertension. Program and abstracts of CHEST 2005: 71st Annual Meeting of the American College of Chest Physicians; October 29 - November 3, 2005; Montreal, Quebec, Canada. Abstract 1722.
- Galiè N, Humbert M, Vachiery J L, et al. Effects of beraprost sodium, an oral prostacyclin analogue, in patients with pulmonary arterial hypertension: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol* 2002;39:1496-1502.
- Barst R, McGoon MD, McLaughlin VV, et al. Beraprost therapy for pulmonary arterial hypertension. *J Am Coll Cardiol*. 2003;41:2119-2125.
- Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005;17;(353):2148-2157.
- Channick RN, Sitbon O, Barst RJ, et al. Endothelin receptor antagonists in pulmonary arterial hypertension. *J Am Coll Cardiol*. 2004;43:62S-67S.
- Liu C. Endothelin receptor antagonists for pulmonary arterial hypertension. *Cochrane Database Syst Rev*. 2005;25:CD004434.
- Barst RJ, Langleben D, Frost A, et al. Sitaxsentan therapy for pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2004;169:441-447.
- Langleben D, Brock T, Dixon R, et al; STRIDE-1 study group. STRIDE 1: Effects of the selective ETA receptor antagonist, sitaxsentan sodium, in a patient population with pulmonary arterial hypertension that meets traditional inclusion criteria of previous pulmonary arterial hypertension trials. *J Cardiovasc Pharmacol*. 2004;44:S80-S84.
- Galiè N, Badesch D, Oudiz R, et al. Ambrisentan therapy for pulmonary arterial hypertension. *J Am Coll Cardiol*. 2005;46:529-535.
- Myogen reports positive top line results for ambrisentan Phase 3 trial in pulmonary arterial hypertension. [press release] Myogen, Inc. 12/12/05. Available at: [investor.myogen.com/phoenix](http://investor.myogen.com/phoenix). Accessed January 24, 2006.
- Hoeper MM, Oudiz RJ, Peacock A, et al. End points and clinical trial designs in pulmonary arterial hypertension: clinical and regulatory perspectives. *J Am Coll Cardiol*. 2004;43(12 Suppl S):48S-55S.
- McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation*. 2002;106:1477-1482.

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# Pulmonary Arterial Hypertension

## Opportunities and Strategies for Medical Intervention

### CME Test

- Although patients may be asymptomatic or have symptoms suggestive of other cardiopulmonary disorders, the most common presenting symptoms in patients with PAH is
  - dyspnea on exertion.
  - dyspnea at rest.
  - syncope.
  - dizziness.
- The index of suspicion for PAH should be greater in which of these patients who present with shortness of breath or unexplained exercise intolerance and the following conditions:
  - renal disease and anemia of chronic disease
  - underlying connective tissue disorders, HIV, or congenital heart disease
  - asthma, aspirin intolerance, or nasal polyps
  - history of exposure to asbestos
- Which of the following is required for the definitive diagnosis of PAH?
  - Doppler echocardiography
  - echocardiography and recognizable symptoms
  - vasodilator testing
  - right heart catheterization
- The primary purpose of acute vasodilator testing is to
  - identify the small percentage of patients who should be treated with calcium channel blockers.
  - exclude concomitant pulmonary disease.
  - identify patients with a poor prognosis.
  - identify patients who will benefit from long-term prostacyclin-based therapy.
- Patients with PAH should undergo acute vasodilator testing by a physician experienced in the management of pulmonary vascular disease with which of the following agents?
  - IV epoprostenol
  - IV adenosine
  - inhaled nitric oxide
  - All of the above.
- The appropriate therapy for acute stabilization of a critically ill patient with PAH is
  - epoprostenol.
  - bosentan.
  - treprostinil.
  - ambrisentan.
- Sildenafil is a phosphodiesterase inhibitor that primarily affects which pathway?
  - prostacyclin pathway
  - nitric oxide pathway
  - endothelin pathway
  - serotonin pathway
- Which of the following correctly describes prostacyclin products and their administration?
  - Treprostinil is short-acting prostacyclin and needs to be administered from six to nine times daily.
  - Beraprost is an inhaled therapy that can cause hypotension.
  - Infusion-site infection is a risk with subcutaneous treprostinil.
  - Iloprost is a short-acting prostacyclin analog delivered by inhalation whose effects are most prominent immediately following administration.
- Which of the following are correctly matched with their mechanism of action?
  - Bosentan: endothelin antagonist selective for the ETA receptor
  - Sitaxasentan: dual endothelin receptor antagonist
  - Ambrisentan: selective endothelin receptor antagonist
  - Beraprost: phosphodiesterase inhibitor
- Which is the most widely used measure of exercise capacity in PAH clinical trials?
  - peak oxygen consumption (VO<sub>2</sub>)
  - six-minute walking distance
  - end-exercise arterial oxygen saturation measured by pulse oximetry
  - treadmill running test

# Pulmonary Arterial Hypertension: Opportunities and Strategies for Medical Intervention

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In order to obtain AMA/PRA category 1 credit, participants are required to

1. Read the learning objectives, review the activity, and complete the self-assessment test.
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### Program Objectives

Having completed this activity, are you better able to:

Strongly Agree      Strongly Disagree

Identify patients at risk for pulmonary arterial hypertension and describe an appropriate approach to diagnosis.      5   4   3   2   1

List the main receptor targets for treatment strategies for pulmonary arterial hypertension.      5   4   3   2   1

Design a therapeutic regimen based on overall risk:benefit considerations, including patient classification and prognostic factors.      5   4   3   2   1

Discuss recent and emerging therapeutic options and how they may fit into the treatment algorithm for patients with PAH, including new agents and the role of add-on therapy.      5   4   3   2   1

### Overall Evaluation

Strongly Agree      Strongly Disagree

The information presented increased my awareness/understanding of the subject.      5   4   3   2   1

The information presented will influence how I practice.      5   4   3   2   1

The information presented will help me improve patient care.      5   4   3   2   1

The faculty demonstrated current knowledge of the subject.      5   4   3   2   1

The activity was educationally sound and scientifically balanced.      5   4   3   2   1

The activity avoided commercial bias or influence.      5   4   3   2   1

Overall, the activity met my expectations.      5   4   3   2   1

I would recommend this activity to my colleagues.      5   4   3   2   1

Based on information presented in the program, I will (check one):

- Do nothing, as the content was not convincing
- Change my practice
- Seek additional information on this topic
- Do nothing, as current practice reflects program's recommendations

If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide us with a brief description of how you plan to do so. You may attach a separate piece of paper.

Please provide any additional comments pertaining to this activity (positives and negatives) and suggestions for improvement.

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Circle the best answer for each question on the CME test.

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| 2.  | A | B | C | D |
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| 4.  | A | B | C | D |
| 5.  | A | B | C | D |
| 6.  | A | B | C | D |
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