The 4th World Symposium on Pulmonary Hypertension: Perspectives for Practice
Guest Editor’s Memo

4th World Symposium Makes History

The 4th World Symposium on Pulmonary Hypertension at Dana Point was a historical event. Composed of 11 working groups in areas of basic science, clinical science, and future perspectives, this 3-day event brought experts in pulmonary vascular disease from all over the world to review the past and current literature, update guidelines and recommendations, and discuss and debate issues regarding the controversies and the future directions in pulmonary arterial hypertension (PAH). What was singularly the most remarkable memory for me was witnessing the collective dedication of the group to reach that elusive, yet definite, goal—finding the cure for PAH, a disease that was recently considered “uniformly fatal.” Indeed, only one had to step into the room to feel the incredible energy and excitement of all the participants—we all felt the past, present, and future of PH converging in that moment.

This meeting marked the 35th anniversary of the 1st World Health Organization Meeting on Pulmonary Hypertension held in Geneva in 1973, a meeting prompted by the outbreak of amiodrox-induced PH. It is a testimony to the unflagging dedication of all involved that we now have 8 FDA-approved therapies with more treatments targeting novel pathways currently being developed.

In putting this issue together, I have had the privilege of working closely with several key members of the working groups. In addition to bringing you a synopsis of several sections, our goals in this issue were to give you an insider’s view on the process of shaping the drafts, personal perspectives on some key controversial issues, and a taste of what we can and should expect at the next World Symposium in 2013. Furthermore, we present a lively roundtable discussion from Drs Robyn Barst, Marc Humbert, Ivan Robbins, and Lewis Rubin, in which they share their experiences and thoughts from the Dana Point meeting and place this symposium in context with the past ones. I hope you enjoy the journey from an insider’s look at the 4th World Symposium from Dana Point.

Myung H. Park, MD
Guest Editor

Editor’s Memo

As a participant in the 4th World Symposium on Pulmonary Hypertension, held February 2008 in Dana Point, California, I was struck by several things—first was the beautiful setting. Although Southern California is no Venice, Italy (site of the 3rd World Symposium), the Pacific Ocean certainly holds its own as far as aesthetics are concerned.

Secondly, I was amazed at how much new knowledge has been garnered since the 3rd World Symposium. Dedicated investigators have continued to help unravel the pathogenesis of pulmonary arterial hypertension (PAH) at the cellular and molecular levels. What happens inside the pulmonary vascular cells that drives the disease process is becoming increasingly clear. Although the complexities of this process are daunting, new “targets” for therapy are being identified in a classic demonstration of “bench-to-bedside” research. On the classification front, increased understanding of specific disease entities and drug exposures and their association with PAH have led to important changes in the classification system. On diagnosis, newer modalities such as biomarkers and advanced imaging (MRI) are gaining a foothold in the evaluation and follow-up of the pulmonary hypertension (PH) patient. Great advances have been made with treatment: at the 3rd World Symposium, 3 drugs were FDA-approved for PAH; at the time of the Dana Point meeting, 6 approved therapies were available. These new options lead to an expanded, evidence-based treatment algorithm.

Perhaps most importantly, I was struck by the sheer number and diversity of (continued on page 63)
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The Mission of the Advances in Pulmonary Hypertension is to serve as the premier forum for state of the art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension. The 2003 Venice revision of the World Health Organization Classification serves as a guide to categories of pulmonary hypertension addressed by this Journal. While focusing on WHO Group I PAH, the other categories (Group II, Left heart disease; Group III, Associated with lung disease and/or hypoxemia; Group IV, Thrombotic and/or Embolic Disease; Group V, Miscellaneous) are also addressed. This mission is achieved by a combination of invited review articles, Roundtable discussions with panels consisting of international experts in PH, and original contributions. In addition, a special section in selected issues entitled “Profiles in Pulmonary Hypertension” recognizes major contributors to the field and serves as an inspiring reminder of the rich and collegial history of dedication to advancing the field.

Objectives
- Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension.
- Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.
- Recognize and preserve the rich history of individuals who have made major contributions to the field via dedication to patient care, innovative research, and furthering the mission of the PH community to cure pulmonary hypertension.

More information on PHA's Scientific Leadership Council and associated committees can be found at: www.PHAssociation.org/SLC/
Advances in Pulmonary Hypertension
Author Guidelines 2009

Scope of Manuscripts
Advances in Pulmonary Hypertension considers the following types of manuscripts for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics in a scholarly fashion and format
- Letters to the Editor
- Clinical Case Studies

Manuscript Submission
Authors are required to submit their manuscripts in an electronic format, preferably by email to the Editor-in-Chief, Richard Channick, MD, rchannick@ucsd.edu. Please provide manuscripts in a word processing program. Images should be submitted electronically as well.

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Contact Information: List all authors, including mailing address, titles and affiliations, phone, fax, and email. Please note corresponding author.

Peer Review and Editing: Manuscripts will be peer-reviewed. Accepted manuscripts will be edited for clarity, spelling, punctuation, grammar, and consistency with American Medical Association (AMA) style.

Manuscript Preparation
Length: Full-length manuscripts should not exceed 4,000 words, including references. Please limit the reference list to 50 citations. Manuscripts should be accompanied by figures and/or tables. Generally, 4 to 5 figures and 2 to 3 tables are preferred for each manuscript. Please include a brief description to accompany these items, as well as a key for all abbreviated words.

Spacing: One space after commas and periods. Manuscripts should be double spaced. Manuscripts should not contain an abstract but an introduction is recommended.


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REVATIO is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability. The efficacy of REVATIO has not been evaluated in patients currently on bosentan therapy.

The use of REVATIO and organic nitrates in any form, at any time, is contraindicated.

Co-administration of REVATIO with potent CYP3A4 inhibitors (eg, ketoconazole, itraconazole, and ritonavir) is not recommended as serum concentrations of sildenafil substantially increase. Co-administration of REVATIO with CYP3A4 inducers, including bosentan; and more potent inducers such as barbiturates, carbamazepine, phenytoin, efavirenz, nevirapine, rifampin, and rifabutin, may alter plasma levels of either or both medications. Dosage adjustment may be necessary.

Before starting REVATIO, physicians should carefully consider whether their patients with underlying conditions could be adversely affected by the mild and transient vasodilatory effects of REVATIO on blood pressure. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of REVATIO to these patients is not recommended. Should signs of pulmonary edema occur when sildenafil is administered, the possibility of associated PVOD should be considered.

The most common side effects of REVATIO (placebo-subtracted) were epistaxis (8%), headache (7%), dyspepsia (6%), flushing (6%), and insomnia (6%). Adverse events were generally transient and mild to moderate.

Caution is advised when PDE5 inhibitors, such as REVATIO, are administered with \( \beta \)-blockers as both are vasodilators with blood pressure lowering effects. REVATIO should be used with caution in patients with anatomical deformation of the penis or patients who have conditions which may predispose them to priapism.

In PAH patients, the concomitant use of vitamin K antagonists and REVATIO resulted in a greater incidence of reports of bleeding (primarily epistaxis) versus placebo. The incidence of epistaxis was higher in patients with PAH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (sildenafil 3%, placebo 2%).

Non-arteritic anterior ischemic optic neuropathy (NAION) has been reported rarely post-marketing in temporal association with the use of PDE5 inhibitors for the treatment of erectile dysfunction, including sildenafil. It is not possible to determine if these events are related to PDE5 inhibitors or to other factors. Physicians should advise patients to seek immediate medical attention in the event of sudden loss of vision while taking PDE5 inhibitors, including REVATIO.

Sudden decrease or loss of hearing has been reported in temporal association with the intake of PDE5 inhibitors, including REVATIO. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors. Physicians should advise patients to seek prompt medical attention in the event of sudden decrease or loss of hearing while taking PDE5 inhibitors, including REVATIO.

REVATIO contains sildenafil citrate, the same active ingredient found in Viagra®

Tracleer (bosentan) is a registered trademark of Actelion Pharmaceuticals.
CONTRAINDICATIONS
Contraindicated with its known effects on the eCB/cB2/GPR55 pathway (CLINICAL PHARMACOLOGY), sildenafil was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/or intermittently, in any form is therefore contraindicated.

WARNINGS
The concomitant administration of the phosphodiesterase inhibitor sildenafil (highly potent PDE5 inhibitor) substantially increases serum concentrations of sildenafil, therefore co-administration with REVATIO is not recommended (see Drug Interactions and DOSE AND ADMINISTRATION).

REVATIO has vasodilator properties, resulting in mild and transient decreases in blood pressure (see PRECAUTIONS). Prior to prescribing REVATIO, physicians should carefully consider whether their patients with certain underlying conditions could be adversely affected by such vasodilatory effects, for example patients with resting hypotension (BP <90/50), or with fluid depletion, severe left ventricular systolic dysfunction, or autonomic dysfunction.

Pharmacokinetic interactions are not clinically significant to cardiovascular or cerebrovascular outcomes in clinical trials. The cardiac risk in patients with left ventricular dysfunction is minimal compared with the risks associated with PDE-5 inhibition (see WARNINGS and DOSAGE AND ADMINISTRATION).

Carcinogenesis, Mutagenesis, Impairment of Fertility
The incidence of epistaxis was higher in patients with PPH secondary to CTD (sildenafil 13%, placebo 0%) than in PPH patients (3%, placebo 0%). The incidence of epistaxis was also higher in sildenafil-treated patients with concomitant oral vitamin K antagonist (9% versus 2% in those not treated with concomitant vitamin K antagonist).

The safety of REVATIO is unknown in patients with bleeding disorders and patients with active peptic ulceration.

Infrequent side effects
Infrequent side effects are not required to be listed if they are not clinically significant. In most cases, the frequency of side effects is not specified when the information is presented in a table. This is because the side effects are rarely severe enough to alter patient management or drug dosing, and therefore the specific frequency of occurrence is not necessary.
participants at the 4th World Symposium. In contrast, the prior 3rd World Symposium seemed somewhat more “exclusive,” with a relatively limited number of global experts meeting in small groups. I believe this expansion in the demographic of the meeting mirrors the disease itself. No longer is PH a rarefied condition treated in a handful of institutions by high-level experts. With the advent of widely available, effective therapy for PAH, we now have the “hot” disease, of interest to a wide-ranging group of healthcare providers. Educational initiatives and outreach, many generated by the Pulmonary Hypertension Association, have clearly taken hold, evidenced by the large and varied audience in Dana Point.

This issue, I hope, will give you the “flavor” of this outstanding meeting. Dr Myung Park, the guest editor, has done a fabulous job gathering several authors, all a co-chair of their respective working groups at the 4th World Symposium. These contributors have provided overviews of their respective committees’ discussions and recommendations. For a complete summary of the symposium, read the supplement in the *Journal of the American College of Cardiology*, July 2009.

I would also like to call your attention to another important, “must read” consensus document from June 2009, published jointly by the American College of Cardiology and American Heart Association, and endorsed by the American Thoracic Society and American College of Chest Physicians. This comprehensive document, edited by Dr Vallerie McLaughlin, summarizes the state of the art in PH.

Finally, in this issue, I am pleased to introduce 4 new features: Article Reviews, Clinical Trials Update, PHRN Corner, and Ask the Expert. These new sections enhance the variety and scope of the journal. I look forward to your feedback, as we are always looking for ways to improve this unique publication. Enjoy.

Richard N. Channick, MD
Editor-in-Chief

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**PHA is Proud to Announce the 2009 Research Grant Award Winners!**

**Recipients of the 2009 PHA Postdoctoral Fellowship Awards**

- **Revathi Rajkumar PhD**
  University of Pittsburgh
  Research: “Genetic Mechanisms of Pulmonary Arterial Hypertension”

- **Gregg Stashenko, MD**
  Duke University, Durham
  Research: “Gene Expression Profiles in Patients with CTEPH Compared to Patients with IPAH”

**Recipient of the 2009 Mentored Patient-Oriented Research Career Development Award (K23)**

- **Stephen Mathai, MD**
  Johns Hopkins University, School of Medicine
  Research: “Neurohormonal Activation in Scleroderma-related Pulmonary Hypertension”

**Recipients of the 2009 Pulmonary Hypertension Association/American Thoracic Society Partnership Grant for Pulmonary Hypertension**

- **Ari Zaiman, MD, PhD**
  Johns Hopkins University School of Medicine
  Research: “Inhibition of TGF beta Signaling in Endothelial Cells; Role in Pulmonary Hypertension”

- **Lunyin Yu, MD**
  Massachusetts General Hospital
  Research: “Role of NHE1 Gene in Development of Pulmonary Hypertension and Vascular Remodeling”

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**Recipient of the 2009 Pulmonary Hypertension Association/American Thoracic Society Partnership Grant for Pulmonary Hypertension**

**To read more about PHA’s research grant program and other research award winners, visit www.PHAssociation.org/support/ResearchFunding.asp**
In the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1, Class II or III symptoms)

Living with PAH can be complicated...

Choosing a therapy should not be.

Please see below for important safety information, including boxed WARNINGS on the possible risk of liver injury and the risk of serious birth defects.

INDICATION: LETAIRIS is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening.

Clinical worsening is defined as the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal due to the addition of other PAH therapeutic agents, or study withdrawal due to early escape.1

Early escape criteria were two or more of the following after a minimum treatment period of 4 weeks: ≥20% decrease in 6-minute walk distance; worsening WHO functional class; worsening right ventricular failure; rapidly progressing cardiac, hepatic, or renal failure; and refractory systolic hypotension <85 mm Hg.1,2

DOSAGE: Initiate treatment at 5 mg once daily with or without food, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated.

Important safety information

WARNINGS: POTENTIAL LIVER INJURY AND CONTRAINDICATION IN PREGNANCY

See full prescribing information for complete boxed WARNINGS.

- Elevations of liver aminotransferases (ALT, AST) have been reported with LETAIRIS and serious liver injury has been reported with related drugs.
- Monitor liver aminotransferases monthly and discontinue LETAIRIS if >5× ULN or if elevations are accompanied by bilirubin >2× ULN or by signs or symptoms of liver dysfunction.
- May cause fetal harm if taken during pregnancy.
- Must exclude pregnancy before the start of treatment.
- Prevent pregnancy thereafter by the use of two reliable methods of contraception.

Important safety information regarding hepatotoxicity

LETAIRIS is not recommended in patients with elevated aminotransferases (>3× ULN) at baseline because monitoring liver injury may be more difficult. If aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, itching, or jaundice) or increases in bilirubin >2× ULN, LETAIRIS treatment should be stopped. There is no experience with the reintroduction of LETAIRIS in these circumstances.

Contraindication

- Do not administer LETAIRIS to a pregnant woman because it can cause fetal harm.

Warnings and precautions

- Decreases in hemoglobin have been observed within the first few weeks of treatment with LETAIRIS; measure hemoglobin prior to initiation, at 1 month, and periodically thereafter.
- Mild to moderate peripheral edema. Peripheral edema occurred more frequently in elderly patients (age ≥65 years) receiving LETAIRIS (29%; 16/56) compared to placebo (4%; 1/28).
- Peripheral edema is a known class effect of endothelin receptor antagonists. In addition, there have been postmarketing reports of fluid retention occurring within weeks after starting LETAIRIS which required intervention with a diuretic, fluid management, or, in some cases, hospitalization for decompensating heart failure.

Drug interactions

- Use caution when LETAIRIS is coadministered with cyclosporine A.
- Use caution when LETAIRIS is coadministered with strong CYP3A inhibitors (e.g., ketoconazole) or CYP2C19 inhibitors (e.g., omeprazole).
- Use caution when LETAIRIS is coadministered with inducers of P-gp, CYPs, and UGTs.

A December 2008

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LETAIRIS offers

Simple dosing

One pill, once a day

Two therapeutically effective doses

- Available in 5 mg and 10 mg tablets
- Initiate treatment at 5 mg once daily, and consider increasing the dose to 10 mg if 5 mg is tolerated

Reliable improvements

Up to +59 m placebo-adjusted mean change from baseline in 6MWD* at 12 weeks with LETAIRIS†1

- LETAIRIS was studied in two 12-week, randomized, double-blind, placebo-controlled, multicenter studies (ARIES-1, N=201, and ARIES-2, N=192);
  - 6MWD was the primary endpoint
    - ARIES-1: +51 m (10 mg, p<0.001) and +31 m (5 mg, p=0.008)
    - ARIES-2: +59 m (5 mg, p<0.001)

Manageable liver function monitoring

Because of the risk of liver aminotransferase (ALT/AST) elevations to at least 3× ULN, liver function testing is required prior to initiation of treatment and at least every month thereafter.

LabSync provides centralized support for all required monthly liver function monitoring associated with LETAIRIS

- LabSync care managers provide a single point of contact for healthcare professionals and patients
- LabSync offers a secure web-based application that allows healthcare professionals instant access to test results
- LabSync provides patients with appointment scheduling and reminder services to assist in managing their monthly testing requirements
- In the postmarketing period, at least one patient receiving another endothelin receptor antagonist (ERA) exhibited late presentation (after 20 months of treatment) of pronounced elevations in aminotransferases and bilirubin levels. This reinforces the importance of monthly liver monitoring for the duration of treatment

because everyday matters

- No significant interactions of LETAIRIS with warfarin or sildenafil have been observed

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=152)</th>
<th>LETAIRIS (n=261)</th>
<th>Placebo-adjusted, %</th>
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<tbody>
<tr>
<td>Peripheral edema</td>
<td>14 (11)</td>
<td>45 (17)</td>
<td>6</td>
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<tr>
<td>Nasal congestion</td>
<td>2 (2)</td>
<td>15 (6)</td>
<td>4</td>
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<tr>
<td>Sinusitis</td>
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<td>8 (3)</td>
<td>3</td>
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<tr>
<td>Flushing</td>
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<td>10 (4)</td>
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<tr>
<td>Palpitations</td>
<td>3 (2)</td>
<td>12 (5)</td>
<td>3</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (1)</td>
<td>9 (3)</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (1)</td>
<td>8 (3)</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (2)</td>
<td>10 (4)</td>
<td>2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4 (3)</td>
<td>11 (4)</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>18 (14)</td>
<td>38 (15)</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: This table includes all adverse events >3% incidence in the combined LETAIRIS treatment group and more frequent than in the placebo group, with a difference of ≥1% between the LETAIRIS and placebo groups.

The efficacy and safety of LETAIRIS were evaluated in two 12-week, randomized, double-blind, placebo-controlled, multicenter studies.

Because of the risks of liver injury and birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP), by calling 1-866-664-LEAP (5327). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS. In addition, LETAIRIS may be dispensed only to patients who are enrolled in and meet all conditions of LEAP.

Please see the brief summary of full prescribing information on next page.


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LETAIRIS is a registered trademark and Gilead and the Gilead logo are trademarks of Gilead Sciences, Inc.
LETARIS® (ambrisentan) 5 mg and 10 mg Tablets

Brief summary* of prescribing information. See full prescribing information. Rx only.

WARNING: POTENTIAL LIVER INJURY
LETARIS® (ambrisentan) can cause elevation of liver aminotransferases (ALT and AST) to at least 3 times the upper limit of normal (ULN). LETARIS treatment was associated with elevations >3× ULN in 12% of patients in placebo-controlled studies and in 2.8% of patients including long-term open-label trials out to one year. One case of aminotransferase elevations >5× ULN has been accompanied by bilirubin elevations >3× ULN. These changes are managed by monitoring and potentially stopping therapy, and by using alternative treatments.

Co-administration of such drugs on ambrisentan exposure is therefore unknown.

Cyclosporine A: Use caution when LETARIS is co-administered with cyclosporine A [see Warnings and Precautions (5.2)].

CYP3A4 inhibitors (e.g., ketoconazole and otherazole, itraconazole, and voriconazole).

The impact of co-administration of such drugs on ambrisentan exposure is therefore unknown.

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Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) in patients with WHO Class II-IV symptoms, to improve exercise ability and decrease the rate of clinical worsening. Patients with WHO Class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these potential benefits are sufficient to offset the risk of liver injury in WHO Class II patients, which may preclude future use as their disease progresses.

*Please see study design and clinical worsening definition on following page.

EARLY: Endothelin Antagonist Trial in Mildly symptomatic PAH patients. PVR: pulmonary vascular resistance.

Please see following pages for important safety information and brief summary of prescribing information including boxed warning.
In functional class II–IV PAH*

Start with Tracleer

- **The only oral PAH therapy** with a placebo-controlled trial conducted solely in WHO functional class II PAH†1
- **The only oral PAH therapy** that significantly reduced the risk of clinical worsening as monotherapy and maintained or improved functional class†1,2
- **The only oral PAH therapy** that significantly improves 4 key hemodynamic parameters—RAP, CI, PVR, and PAP‡3
- **The only oral PAH therapy** with over 7 years of PAH experience, prescribed to over 55,000 patients4
- Actelion—over 10 years of dedication and commitment to the PAH community

*Please see previous page for full indication.
†EARLY: Endothelin Antagonist tRial in miLDly symptomatic PAH patients. Randomized, double-blind, placebo-controlled trial of Tracleer 125 mg BID in patients with functional class II PAH (N=185). Patients were randomized to Tracleer (62.5 mg BID, 125 mg BID) or placebo. Trial duration was 6 months. Concomitant use of anticoagulants and calcium channel blockers was allowed. Clinical worsening events were defined as death from any cause (during the treatment period or as the outcome of a treatment-emergent adverse event that led to permanent discontinuation of study treatment), hospitalization due to PAH complications, or symptomatic progression of PAH. Patients experiencing worsening events: n=3, Tracleer; n=13, placebo (p=0.01). At week 24, 7.6% absolute risk reduction in clinical worsening; number needed to treat (NNT) = 13 (NNT = 1 ÷ absolute risk reduction). Percentage of patients deteriorating in functional class status at month 6: 3.4%, Tracleer; 12.2%, placebo (p=0.03). Change from baseline in pulmonary vascular resistance (PVR) at month 6: −23% treatment effect (p<0.05).1,2
‡Study 351 Randomized, double-blind, placebo-controlled study of Tracleer 125 mg BID in patients with WHO functional class III or IV PAH (N=32). p<0.02 for change in cardiac index (CI), right atrial pressure (RAP), pulmonary arterial pressure (PAP), and pulmonary vascular resistance (PVR).1,3

**Important safety information**

Because of the associated risks, Tracleer may be prescribed only through the Tracleer Access Program.

**Potential for serious liver injury** (including, after prolonged treatment, rare cases of liver failure and unexplained hepatic cirrhosis in a setting of close monitoring)—Liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter. **High potential for major birth defects**—Pregnancy must be excluded and prevented through the use of reliable forms of birth control; monthly pregnancy tests should be obtained.

**Contraindicated for use with cyclosporine A and glyburide.**

Please visit www.TRACLEER.com to learn more about Tracleer and PAH.
Please see following pages for brief summary of prescribing information.
Tracleer is available as 62.5 mg and 125 mg film-coated, unscored tablets for oral administration. 62.5 mg tablets: film-coated, round, biconvex, orange-white tablets, embossed with identification marking “3”.

125 mg tablets: film-coated, oval, biconvex, orange-white tablets, embossed with identification marking “125”.

**CONTRAINDICATIONS**

Use of Tracleer is contraindicated in females who are or may become pregnant. While there are no adequate and well controlled studies in pregnant females, animal studies show that Tracleer is teratogenic. The potential risk to the fetus warrants the use of effective contraceptive measures in women of reproductive potential during treatment with Tracleer. If the patient becomes pregnant while receiving Tracleer, the patient should be apprised of the potential hazard to the fetus.

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**Dosage Forms and Strengths**

- **Table:**Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Elevations

<table>
<thead>
<tr>
<th>Aminotransferase Levels</th>
<th>Treatment and monitoring recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 2 and ≤ 5 x ULN</td>
<td>Confirm by another aminotransferase test, if confirmed, reduce the daily dose to 62.5 mg twice daily or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate (see below).</td>
</tr>
<tr>
<td>&gt; 5 x ULN</td>
<td>Confirm by another aminotransferase test, if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment (see below).</td>
</tr>
<tr>
<td>≥ 10 x ULN</td>
<td>Treatment should be stopped and re-introduction of Tracleer should not be considered. There is no experience with re-introduction of Tracleer in these circumstances.</td>
</tr>
</tbody>
</table>

If Tracleer is re-introduced it should be at the starting dose; aminotransferase levels should be checked within 3 days and thereafter according to the recommendations above.

- **Use in Females of Childbearing Potential**

Initiate treatment in females of child-bearing potential only after a negative pregnancy test and only in females of child-bearing potential who are using two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNG 20 IUS inserted, in which case no other contraception is needed. Hormonal contraceptives, use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNG 20 IUS inserted, in which case no other contraception is needed.

- **Use in Patients with Pre-existing Hepatic Impairment**

Tracleer should be administered to patients with hepatic impairment only if the benefit outweighs the risk. Further evaluation should be undertaken to determine the cause, such as Tracleer or underlying heart failure, and the possible need for discontinuation of Tracleer therapy.

- **Decrease in Sperm Counts**

An open-label, single arm, multicenter, safety study evaluated the effect on testicular function of Tracleer in patients with pulmonary arterial hypertension (PAH) (N = 98). Twenty-three completed the study and 2 discontinued due to adverse events not related to treatment. There was a significant decrease in sperm count of at least 50% in 23% of the patients. Based on these findings and preclinical data from endothelin receptor antagonists, it cannot be exclusion that endothelin receptor antagonists such as Tracleer have an adverse effect on spermatogenesis.

- **Treatment Discontinuation**

There is limited experience with abrupt discontinuation of Tracleer. No evidence for acute rebound has been observed. Nevertheless, to avoid the potential for clinical deterioration, gradual dose reduction (62.5 mg twice daily for 3 to 7 days) should be considered.

- **Contraception**

Tracleer is available only through a special restricted distribution program called the Tracleer Access Program (T.A.P.). Only prescribers and

- **Interactions**

- **Drug**

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pharmacies registered with T.A.P may prescribe and distribute Tracleer. In addition, Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P. Information about Tracleer and T.A.P can be obtained by calling 1-866-228-3546.

To enroll in T.A.P, prescribers must complete the T.A.P. Tracleer (bosentan) Enrollment and Renewal Form for each patient (see Enrolment and Renewal Form for full prescribing physician agreement) indicating agreement to:

- Review and understand the communication and educational materials for prescribers regarding the risks of Tracleer.
- Review and discuss the Tracleer Medication Guide and the risks of bosentan (including the risks of teratogenicity and hepatotoxicity) with every patient prior to prescribing Tracleer.
- Review pretreatment liver function tests (ALT/AST/bilirubin) and, for females of childbearing potential, confirm that the patient is not pregnant.
- Agree to order and monitor monthly liver function tests and, for females of childbearing potential, pregnancy tests.
- Enroll all patients in T.A.P and renew patients’ enrollment annually thereafter.

Education and counsel females of childbearing potential to avoid contraceptive failure, as defined on the Tracleer Enrollment and Renewal Form, during treatment with Tracleer and for one month after treatment discontinuation.

- Confirm that patients who fail to comply with the program requirements.

- Notify Action Pharmaceuticals US, Inc. of any adverse events, including liver injury, and any pregnancy during Tracleer treatment.

Throughout treatment and for one month after stopping Tracleer, females of childbearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNG 20 IUS inserted, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving Tracleer.

ADVERSE REACTIONS

The following important adverse reactions are described elsewhere in the labeling:

- Potential liver injury [see Boxed Warning and Warnings and Precautions]

- Fluid retention [see Warnings and Precautions]

Clinical Studies Experience

Safety data on bosentan were obtained from 13 clinical studies (9 placebo-controlled and 4 open-label) in 810 patients with pulmonary arterial hypertension and other diseases. Doses up to 8 times the currently recommended (200 mg twice daily) were administered for a variety of durations. Of these, 279 patients were exposed to bosentan in these trials ranged from 1 day to 4.1 years (N=94 for 1 year; N=41 for 1.5 years and N=39 for 2 years). The most common adverse events in patients suffering from pulmonary arterial hypertension (N=208) to bosentan ranged from 1 day to 1.7 years (N=174 more than 6 months and N=28 more than 12 months).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Treatment discontinuations due to adverse events other than those related to pulmonary hypertension during clinical trials are provided. All patients with pulmonary arterial hypertension were more frequent on bosentan (8%; 15/258 patients) than on placebo (3%; 5/172 patients). In this database, the only discontinuation rates -1% did not change compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The adverse drug events that occurred in 23% of the bosentan-treated patients and were more common on placebo in bosentan-controlled trials in pulmonary arterial hypertension at doses of 125 or 250 mg twice daily are shown in Table 2.

Hormonal Contraceptives

All reported events (at least 3%) are included except those too general to be informative, and those not attributable to bosentan exposure.

Because these adverse reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Tracleer exposure:

An increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with bosentan and a selective serotonin reuptake inhibitor. Therefore, the concomitant administration of Tracleer and an antidepressant is contraindicated, and alternative hypoglycemic agents should be considered (see Contraindications).

An increased risk of hepatotoxicity has been observed in patients receiving concomitant bosentan and cyclosporine at plasma concentrations of bosentan greater than 50 ng/mL. The use of cyclosporine in these patients has not been studied and should be avoided. The plasma concentrations of cyclosporine should be monitored closely during bosentan treatment. The dose of cyclosporine should be reduced if the trough concentration of cyclosporine rises to more than 500 ng/mL.

An increased risk of osmolality-related adverse events was observed in patients receiving concomitant therapy with bosentan and a thiazide diuretic. Therefore, the concomitant administration of Tracleer and a thiazide diuretic is contraindicated (see Contraindications).

An increased risk of achieving a therapeutic effect of bosentan with bosentan and rifampin should be considered (see Contraindications).

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Bosentan was teratogenic in rats given oral doses two times the maximum recommended human dose (MRHD) (on a mg/m² basis). In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses 2 and 10 times the MRHD (on a mg/m² basis). Although birth defects were not observed in rabbits given oral doses of up to the equivalent of 10.5 mg/kg/day in a 70 kg person, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs (see Nonclinical Toxicology).

Nursing Mothers

It is not known whether Tracleer is excreted into human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Tracleer, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and efficacy in pediatric patients have not been established.

Geriatric Use

Clinical studies of Tracleer did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Clinical experience has not identified differences in responses between elderly and younger patients. In general, caution should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group.

Hepatic Impairment

Because there is in vitro and in vivo evidence that the main route of excretion of bosentan is biliary, liver impairment could be expected to increase exposure (C₀ and AUC) of bosentan. Mild liver impairment was shown not to impact the pharmacokinetics of Bosentan. The influence of moderate or severe liver impairment on the pharmacokinetics of Tracleer has not been evaluated. There are no specific data to guide dosing in hepatitically impaired patients; caution should be exercised in patients with mildly impaired liver function. Tracleer should generally be avoided in patients with moderate or severe liver impairment (see Dosage and Administration, Warnings and Precautions).

Renal Impairment

The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosing adjustment.

Patients with Low Body Weight (see Dosage and Administration).

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males as doses as low as 450 mg/kg/day (about 8 times the maximum recommended human dose (MRHD)) of 125 mg twice daily, on a mg/m² basis. In the same study, doses greater than 2000 mg/kg/day (about 32 times the MRHD) were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses as low as 500 mg/kg/day (about 16 times the MRHD). In a comprehensive battery of in vitro tests (the microbial mutagenesis assay, the unscheduled DNA synthesis assay, the V-79 mammalian cell mutagenesis assay, and human lymphocyte assay) and an in vivo mouse micronucleus assay, there was no evidence for any mutagenic or clastogenic activity of bosentan.

Reproductive and Developmental Toxicology

Bosentan was teratogenic in rats given oral doses 180 mg/kg/day. In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses of 125 mg/kg/day. In the same study, incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses as low as 500 mg/kg/day (about 16 times the MRHD). In a comprehensive battery of in vitro tests (the microbial mutagenesis assay, the unscheduled DNA synthesis assay, the V-79 mammalian cell mutagenesis assay, and human lymphocyte assay) and an in vivo mouse micronucleus assay, there was no evidence for any mutagenic or clastogenic activity of bosentan.

Reproductive and Developmental Toxicology

Bosentan was teratogenic in rats given oral doses two times the maximum recommended human dose (MRHD) (on a mg/m² basis). In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses 2 and 10 times the MRHD (on a mg/m² basis). Although birth defects were not observed in rabbits given oral doses of up to the equivalent of 10.5 mg/kg/day in a 70 kg person, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs (see Nonclinical Toxicology).

Impairment of Fertility/Teatific Function

The development of testicular tubular atrophy and impaired fertility has been linked with the chronic administration of certain endothelin receptor antagonists in rodents. Treatment with bosentan at oral doses of up to 1500 mg/kg/day (50 times the MRHD on a mg/m² basis) or intravenous doses up to 40 mg/kg/day had no effects on sperm count, sperm motility, mating performance or fertility in male and female rats. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as 125 mg/kg/day (about 4 times the MRHD and the lowest doses tested) for two years but not at doses as high as 1000 mg/kg/day (about 50 times the MRHD) for 6 months. Effects on sperm count and motility were evaluated only in the much shorter duration fertility studies in which males had been exposed to the drug for 4-6 weeks. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to 4500 mg/kg/day (about 75 times the MRHD) or in dogs treated up to 12 months at doses up to 500 mg/kg/day (about 50 times the MRHD).

PATIENT COUNSELING INFORMATION

Advise patients to consult the Medication Guide on the safe use of Tracleer.

Important Information

- Monthly monitoring of serum aminotransferases
  - The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases.
- Pregnancy testing and avoidance of pregnancy
  - Patients should be advised that Tracleer is likely to cause birth defects based on animal studies.
  - Tracleer treatment should only be initiated in females of childbearing potential following a negative pregnancy test. Females of childbearing potential must have monthly pregnancy tests and need to use two different forms of contraception while taking Tracleer and for one month after discontinuing Tracleer. Females who have a tubal ligation or a Copper T 380A IUD or LNG 20 IU can use these contraceptive methods alone. Patients should be instructed to immediately contact their physician if they suspect they may be pregnant and should seek contraceptive advice from a gynecologist or similar expert as needed.
- Drug Interactions
  - The physician should discuss with the patient possible drug interactions with Tracleer, and which medications should not be taken with Tracleer. The physician should discuss the importance of disclosing all concomitant or new medications.

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References for previous pages:
PHA’s 9th International Pulmonary Hypertension Conference and Scientific Sessions

Riding the Wave to a Cure

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CALL FOR ABSTRACTS
Submission Deadline: March 10, 2010

Submit your abstract for the poster session at PHA’s 9th International Pulmonary Hypertension Conference and Scientific Sessions in the areas of clinical science (including treatment) and basic science. Four abstracts will be selected for oral presentation and an award will be given to the top two abstracts. Summaries of top presentations will be published in a future issue of Advances in Pulmonary Hypertension. Although PHA encourages the submission of original abstracts, abstracts submitted to PHA do not need to be original work. Submit your abstract to Medical@PHAssociation.org.
Indications:
REMODULIN® (treprostinil sodium) Injection is indicated for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms to diminish symptoms associated with exercise. It may be administered as a continuous subcutaneous infusion or continuous intravenous infusion; however, because of the risks associated with chronic indwelling central venous catheters, including serious blood stream infections, continuous intravenous infusion should be reserved for patients who are intolerant of the subcutaneous route, or in whom these risks are considered warranted.

In patients with pulmonary arterial hypertension requiring transition from Flolan® (epoprostenol sodium), REMODULIN is indicated to diminish the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition.

Important Safety Information:
Chronic intravenous infusions of REMODULIN are delivered using an indwelling central venous catheter. This route is associated with the risk of blood stream infections (BSI) and sepsis, which may be fatal. REMODULIN should be used only by clinicians experienced in the diagnosis and treatment of PAH. REMODULIN is a potent pulmonary and systemic vasodilator. Initiation of REMODULIN must be performed in a setting with adequate personnel and equipment for physiological monitoring and emergency care. Therapy with REMODULIN may be used for prolonged periods, and the patient’s ability to administer REMODULIN and care for an infusion system should be carefully considered.

Dose should be increased for lack of improvement in, or worsening of, symptoms and it should be decreased for excessive pharmacologic effects or for unacceptable infusion site symptoms. Abrupt withdrawal or sudden large reductions in dosage of REMODULIN may result in worsening of PAH symptoms and should be avoided. Caution should be used in patients with hepatic or renal insufficiency.

The most common side effects of REMODULIN included those related to the method of infusion. For subcutaneous infusion, infusion site pain and infusion site reaction (redness and swelling) occurred in the majority of patients. These symptoms were often severe and could lead to treatment with narcotics or discontinuation of REMODULIN. For intravenous infusion, line infections, sepsis, arm swelling, tingling sensations, bruising, and pain were most common. General side effects (≥5% more than placebo) were diarrhea, jaw pain, vasodilation, and edema.

References:

For important safety and other information, please see brief summary of full prescribing information on the back of this page.

REMODULIN® (treprostinil sodium) Injection
Empowering Prostacyclin

Joanne
REMODULIN patient
Infused with POSSIBILITIES
When initial PAH therapy loses its momentum, think REMODULIN
Remodulin® (treprostinil sodium) Injection

Brief Summary
The following is a brief summary of the full prescribing information on Remodulin (treprostinil sodium) Injection. Please review the full prescribing information prior to prescribing Remodulin.

Indications and Usage
Pulmonary Arterial Hypertension in Patients With NYHA Class II-IV Symptoms
Remodulin is indicated for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms to diminish symptoms associated with exercise. It may be administered as a continuous subcutaneous infusion or intravenous infusion; however, because of the risks associated with chronic indwelling central venous catheters, including serious blood stream infections, continuous intravenous infusion should be reserved for patients who are intolerant of the subcutaneous route, or in whom these risks are considered warranted.

Pulmonary Arterial Hypertension in Patients Requiring Transition From Flotrin®
In patients with pulmonary arterial hypertension requiring transition from Flotran (epoprostenol sodium), Remodulin is indicated to diminish the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition.

WARNINGS AND PRECAUTIONS
Risks Associated With the Drug Delivery System
Continuous intravenous infusions of Remodulin are delivered using an indwelling central venous catheter. This route is associated with the risk of blood stream infections (BSIs) and sepsis, which may be fatal. In a post-marketing study of IV treprostinil (n=47), there were seven catheter-related line infections during approximately 35 patient years, or about 1 BSI event per 5 years of use. A CDC survey of seven sites that used IV treprostinil for the treatment of PAH found approximately 1 BSI (defined as any positive blood culture) event per 3 years of use.

General Conditions of Use
Remodulin should be used only by clinicians experienced in the diagnosis and treatment of PAH. Remodulin is a potent pulmonary and systemic vasodilator. Initiation of Remodulin must be performed in a setting with adequate personnel and equipment for physiological monitoring and emergency care. Therapy with Remodulin may be used for prolonged periods, and the patient’s ability to administer Remodulin and care for an infusion system should be carefully considered.

Dose Modification
Dose should be increased for lack of improvement in, or worsening of, symptoms and it should be decreased for excessive pharmacologic effects or for unacceptable infusion site symptoms.

Abrupt Withdrawal or Sudden Large Dose Reduction
Abrupt withdrawal or sudden large reductions in dosage of Remodulin may result in worsening of PAH symptoms and should be avoided.

Hepatic and Renal Insufficiency
Caution should be used in patients with hepatic or renal insufficiency.

Adverse Reactions
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates may be difficult to compare with rates observed in other clinical studies and at different treatment settings.

Adverse Events With Subcutaneously Administered Remodulin
Patients receiving Remodulin as a subcutaneous infusion reported a wide range of adverse events. Many of the events were associated with the underlying disease (dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor). During clinical trials with subcutaneous infusion of Remodulin, infusion site pain and reaction were the most common adverse events among those treated with Remodulin. Infusion site reaction was defined as any local adverse event other than pain or bleeding/bruising at the infusion site and included symptoms such as erythema, induration or rash. Infusion site reactions were sometimes severe and could lead to discontinuation of treatment.

Percentages of subjects reporting subcutaneous infusion site adverse events

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Placebo</th>
<th>Remodulin</th>
<th>Placebo</th>
<th>Remodulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>38</td>
<td>2</td>
<td>39</td>
<td>6</td>
</tr>
<tr>
<td>Requiring narcotics*</td>
<td>NA†</td>
<td>NA†</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>

* Based on prescriptions for narcotics, not actual use
† medications used to treat infusion site pain were not distinguished from those used to treat site reactions

Adverse Reactions During Chronic Dosing
The following table lists adverse events that occurred at a rate of at least 3% and were more frequent in patients treated with subcutaneous Remodulin than with placebo in controlled trials in PAH.

Adverse Events in Controlled 12-Week Studies of Patients with PAH, Occurring with at Least 3% Incidence and More Common on Subcutaneous Remodulin than on Placebo

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Remodulin (N=236)</th>
<th>Placebo (N=233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction (%)</td>
<td>Percent of Patients</td>
<td>Percent of Patients</td>
</tr>
<tr>
<td>Infusion Site Pain</td>
<td>53</td>
<td>27</td>
</tr>
<tr>
<td>Infusion Site Reaction</td>
<td>85</td>
<td>32</td>
</tr>
<tr>
<td>Headache</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>Rash</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Jaw Pain</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Edema</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

Reported adverse events (at least 3%) are included those too general to be informative, and those not plausibly attributable to the use of the drug, because they were associated with the condition being treated or are very common in the treated population.

Adverse Events Attributable to the Drug Delivery System
In controlled studies of Remodulin administered subcutaneously, there were no reports of infection related to the drug delivery system. There were 187 infusion system complications reported in 28% of patients (23% Remodulin, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. Eight of these patients (4 Remodulin, 4 Placebo) reported non-serious adverse events resulting from infusion system complications. Adverse events resulting from problems with the delivery system were typically related to either symptoms of excess Remodulin (e.g., nausea) or return of PAH symptoms (e.g., dyspnea). These events were generally resolved by correcting the delivery system pump or infusion set problem such as replacing the syringe, repairing the pump, or straightening a cramped infusion line. Adverse events resulting from problems with the delivery system did not lead to clinical instability or rapid deterioration. In addition to these adverse events due to the drug delivery system during subcutaneous administration, the following adverse events may be attributable to the IV mode of infusion including arm swelling, phlebitis, headaches and pain.

Post-Marketing Experience
In addition to adverse reactions reported from clinical trials, the following events have been identified during post-marketing use of Remodulin from a population of unknown size, estimates of frequency cannot be made. The following events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, and potential connection to Remodulin. These events are thromboembolism associated with peripheral intravenous infusion, thrombocytopenia and bone pain. In addition, generalized rashes, sometimes macular or papular in nature, and cellulitis have been infrequently reported.

Drug Interactions
Reduction in blood pressure caused by Remodulin may be exacerbated by drugs that themselves alter blood pressure, such as diuretics, antihypertensive agents, or vasodilators. Since Remodulin inhibits platelet aggregation, there is also a potential for increased risk of bleeding, particularly among patients maintained on anticoagulants. During clinical trials, Remodulin was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, anti-inflammatories, opioids, corticosteroids, and other medications. Remodulin has not been studied in conjunction with Flotran or Tracleer® (bosentan).

Effect of Other Drugs on Remodulin
Warfarin - Analgesic doses of acetaminophen, 1000 mg every 6 hours for seven doses, did not affect the pharmacokinetics of Remodulin, at a subcutaneous infusion rate of 15 ng/kg/min.

Effect of Remodulin on Other Drugs
In vitro studies: Remodulin did not significantly affect the plasma protein binding of normally observed concentrations of digoxin and warfarin.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category B - In pregnant rats, continuous subcutaneous infusions of treprostinil sodium during organogenesis and late gestational development, at rates as high as 300 ng treprostinil/kg/min (about 117 times the starting human rate of infusion, on a ng/m² basis, and about 16 times the average rate achieved in clinical trials), resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous subcutaneous infusions of treprostinil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng treprostinil/kg/min (about 41 times the starting human rate of infusion, on a ng/m² basis), and 53% of the fetuses had major congenital anomalies. Continuous subcutaneous infusion of treprostinil from implantation to the end of lactation, at rates of up to 450 ng treprostinil/kg/min, did not affect the growth and development of offspring. Because animal reproduction studies are not always predictive of human response, Remodulin should be used during pregnancy only if clearly needed.

Labor and Delivery
No treprostinil sodium treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinil sodium on labor and delivery in humans is unknown.

Nursing Mothers
It is not known whether treprostinil is excreted in human milk or absorbed systemically after intravenous drug administration. Because many drugs are excreted in human milk, caution should be exercised when Remodulin is administered to nursing women.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established. Clinical Studies of Remodulin did not include sufficient numbers of patients aged <16 years to determine whether they respond differently from older patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, and cardiac function, and of concomitant disease or other drug therapy.

Effect of Remodulin on Other Drugs
Remodulin clearance is reduced in patients with hepatic insufficiency. In patients with mild or moderate hepatic insufficiency, the initial dose of Remodulin should be decreased to 0.625 mg/kg/min ideal body weight and should be increased cautiously. Remodulin has not been studied in patients with severe hepatic insufficiency.

No studies have been performed in patients with renal insufficiency. No specific advice about dosing in patients with renal impairment can be given.

OVERDOSAGE
Signs and symptoms of overdose with Remodulin during clinical trials are extensions of its dose-limiting pharmacologic effects and include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withdrawal of Remodulin.

In controlled clinical trials, seven patients received some level of overdose and in open-label follow-on treatment seven additional patients received an overdose; these occurrences resulted from accidental bolus administration of Remodulin, errors in pump programmed rate of administration, and accidental omission of drug. In one case, an incorrect dose of Remodulin was administered, and one patient received an incorrect dose of Remodulin. Removal of Remodulin has not been studied in patients with severe hepatic insufficiency.

No studies have been performed in patients with renal insufficiency. No specific advice about dosing in patients with renal impairment can be given.

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Rx only
September 2009

Refer to Full Package Insert for Complete Information
Advances in Pulmonary Hypertension

Program Overview
Pulmonary arterial hypertension (PAH), an incurable disease, is characterized by medial hypertrophy, intimal fibrosis, and in situ thrombi in small muscular pulmonary arteries. PAH was considered a rapidly fatal illness with a median survival of 2.8 years in the 1980s when no evidence-based therapies were available. Since then the treatment of this disease has made tremendous advances, and the last 10 years have seen the discovery of new medications that have positively influenced the prognosis and survival of patients with PAH.

This self-study activity is based on 6 articles that review the outcomes of the 4th World Symposium on Pulmonary Hypertension.

This activity is jointly sponsored by the University of Michigan Medical School and the Pulmonary Hypertension Association and supported by an unrestricted education grant from Actelion Pharmaceuticals US, Inc, Gilead Sciences, Inc, Pfizer, Inc, and United Therapeutics Corporation.

Target Audience
This self-study activity is appropriate for cardiologists, pulmonologists, rheumatologists, and other physicians who treat patients with pulmonary hypertension.

Learning Objectives
Upon completion of this activity participants will be able to:
1. Review modifications from the 4th World Symposium on Pulmonary Hypertension in Dana Point, California
2. Identify changes to the PH classification system and current understanding in genetics in PAH
3. Understand the rationale behind current treatment guideline recommendations
4. Assess latest recommendations in diagnosing PAH
5. Know current understanding in secondary forms of PH

Self-Assessment Examination
See pages 87 and 88 for self-assessment questions, answer key, and evaluation form.

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Agenda
Epidemiology and Classification of Pulmonary Hypertension
Ivan M. Robbins, MD

Summary of Pulmonary Hypertension Genetics and Genomics
Greg Elliott, MD

Diagnosis and Assessment of Pulmonary Arterial Hypertension: A Glance at the Output From the Dana Point Conference
Adam Torbicki, MD, PhD

Updated Evidence-Based Treatment Algorithm in Pulmonary Arterial Hypertension
Robyn J. Barst, MD

Diagnosis, Assessment, and Treatment of Nonpulmonary Arterial Hypertension Pulmonary Hypertension
Marius M. Hoeper, MD

Future Perspectives for the Treatment of Pulmonary Arterial Hypertension
Karen A. Fagan, MD
**Accreditation Statement**
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 the University of Michigan Medical School and the Pulmonary Hypertension Association. The University of Michigan is accredited by the ACCME to provide continuing medical education to physicians.

**Credit Designation**
The University of Michigan Medical School designates this activity for a maximum of 2.0 AMA PRA Category 1 Credits™. Physicians should claim credit commensurate with the extent of their participation in the activity.

**Instructions for Earning Credit**
This activity is a self-study program; a self-assessment examination is included on page 87 to help physicians review important points. A form is also included on page 88 for physicians to evaluate the CME activity. Completion of this activity involves reading the journal and completing the self-assessment examination and evaluation form, which may take up to 2 hours. Credits for this self-study program are available from September 25, 2009 through September 25, 2010. There is no fee for this program.

Please note that this self-study program may also be viewed online at: http://www.cme.med.umich.edu.

**University of Michigan Privacy Statement**
http://www.cme.med.umich.edu/privacy.asp

**Sponsorship**
This CME self-study program is jointly sponsored by the University of Michigan Medical School and the Pulmonary Hypertension Association.

**Support**
This CME self-study program is supported by an educational grant from Actelion Pharmaceuticals US, Inc., Gilead Sciences, Inc., Pfizer, Inc., and United Therapeutics Corporation.

**Oversight and Accreditation**
Arlene Bradford, BA
Assistant Director
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**Disclosures**
The Accreditation Council for Continuing Medical Education and the Association of American Colleges have standards and guidelines to ensure that individuals participating in CME activities are aware of relationships between authors and commercial companies that could potentially affect the information presented. To be disclosed to participants are all personal financial relationships with a commercial interest whose products are relevant to the content of this CME activity. The University of Michigan Medical School follows these national policies to ensure balance, independence, objectivity, and scientific rigor in all its CME activities. Each author was asked to complete a disclosure information form for this activity. Disclosures are reported below.

Ivan Robbins, MD, has no declarable relationships.

C. Gregory Elliott, MD, has received grants from Pfizer, Encysive, Actelion, Eli Lilly/ICOS, and United Therapeutics for contracts on which he is the site principal investigator. He serves as a consultant to Actelion as a member of the steering committee for the REVEAL registry.

Adam Torbicki, MD, has served as a consultant for Eli Lilly, GSK, and mondoBiotech. He has received speakers’ honoraria from Bayer Schering, Eli Lilly, and Sanofi-Aventis. He has conducted research supported by Actelion, Bayer Schering, Bristol-Meyers Squibb, Eli Lilly, GSK, mondoBiotech, and Pfizer.

Robyn J. Barst, MD, has received grants or outside funding from Actelion, GSK, Gilead, United Therapeutics, Pfizer, and Novartis. She is an advisory board member for Actelion, Pfizer, GSK, Gilead, and Eli Lilly. She has a paid consulting relationship with Actelion, Pfizer, Eli Lilly, GSK, and Gilead.

Marius M. Hoeper, MD, has received payments for speaking at conferences and consultancies from Actelion, Bayer, Gilead, GSK, Pfizer, LungRx, and Novartis.

Karen A. Fagan, MD, has received payments from Gilead for serving on a speaker panel, advisory board, and research committee.

Myung H. Park, MD, has received payment for serving as a consultant and advisory board member for Actelion, Gilead, and United Therapeutics.

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Dr Chan has no relevant personal financial relationships to disclose.
During the 4th World Symposium on Pulmonary Hypertension held last year in Dana Point, California, the consensus agreement of experts worldwide was to maintain the general philosophy and organization of the previous Evian and Venice classifications. However, a majority of experts felt that modification of the Venice classification was required in order to accurately reflect new information published over the past 5 years and to clarify some areas that were unclear. Important changes included in the Dana Point classification are summarized here. These changes should more accurately reflect the disease processes and allow for better communication among investigators.

**Group 1: Pulmonary Arterial Hypertension**

Pulmonary arterial hypertension (PAH) has been the focus of the categorization of pulmonary hypertension (PH) since the first classification in 1973. A number of modifications of the subgroups of PAH were made in the Dana Point classification.

When PAH occurs in a familial context, germline mutations in the bone morphogenetic protein receptor 2 (BMPR2) gene, a member of the transforming growth factor beta signalling family, can be detected in about 70% of cases. BMPR2 mutations have also been detected in 11% to 40% of apparently idiopathic cases without any family history. Thus, the distinction between idiopathic and familial BMPR2 mutations is artificial as all patients with a BMPR2 mutation have heritable disease whether the patient is the first identified case, possibly with a *de novo* mutation, or whether other family members were previously diagnosed with PAH. In addition, no BMPR2 mutation has been identified in up to 20% of families with PAH. Thus, it was decided to abandon the term “familial PAH” in the new classification and replacing it with the term “heritable.”

Additional changes in group 1 were also implemented in the Dana Point classification. The classification of PAH associated with congenital heart disease was modified to better define each condition. Hemolytic anemias, either inherited or acquired, have been reclassified as their own subcategory of PAH, based in large part upon growing awareness of PH in patients with sickle cell disease. Finally, schistosomiasis has been moved from the thromboembolic group to a subgroup of PAH.

**Risk Factors for the Development of Pulmonary Arterial Hypertension**

Two important changes regarding risk factors for PAH were discussed. First, based primarily on a large single-center case-control study, methamphetamine use appears to be a likely risk factor for the development of PAH. Second, although no increased risk of developing PAH with the use of selective serotonin reuptake inhibitors (SSRIs) was found in a multicenter epidemiological study, use of SSRIs in pregnant women was reported to increase the risk (OR 6.1) in the offspring of developing persistent pulmonary hypertension of the newborn (PPHN). Therefore, SSRI use in pregnancy is a potential risk factor for PPHN.

**Group 2: Pulmonary Hypertension Owing to Left Heart Disease**

This group has been modified to reflect the growing importance of left ventricular diastolic dysfunction as a cause of pulmonary venous hypertension. Subcategories in the new classification are: left heart systolic dysfunction, left heart diastolic dysfunction, and left heart valvular disease. No formal recommendations were made concerning patients with left heart disease and “out-of-proportion” PH, and there are currently no clinical trials that have shown benefit with PAH-approved medications in this group of patients.

**Group 3: Pulmonary Hypertension Owing to Lung Diseases and/or Hypoxia**

The primary modification within this group was to add another category of lung disease characterized by a mixed obstructive and restrictive pattern. This is a newly reported syndrome, characterized by the combination of pulmonary fibrosis (mainly of the lower zones of the lung) and emphysema (mainly of the upper zones of the lung) and has a reported prevalence of PH of almost 50%.

**Group 4: Chronic Thromboembolic Pulmonary Hypertension**

This group has been simplified to include only chronic thromboembolic PH (CTEPH). Other rare forms of obstruction of the pulmonary vasculature, such as pulmonary artery sarcoma, have...
been reclassified into Group 5. In addition, the distinction between proximal and distal disease has been removed as this may be quite difficult to determine and is often dependent upon the experience of each individual center. Presently there is no consensus among experts regarding the distinction between proximal and distal CTEPH. It is strongly recommended that patients with suspected or confirmed CTEPH should be referred to a center with expertise in the management of CTEPH to consider feasibility of pulmonary thromboendarterectomy.

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**Summary of Pulmonary Hypertension Genetics and Genomics**

Greg Elliott, MD  
University of Utah School of Medicine

The 4th World Symposium on Pulmonary Hypertension convened a group of investigators to define the current state of knowledge with respect to the genetics and genomics of pulmonary arterial hypertension (PAH), and to provide suggestions for future investigations. The consensus statement appears in a supplement to the *Journal of the American College of Cardiology* (Machado, 2009;54:S32-S42). In this communication, I will summarize several of the key clinical points made in the consensus statement, provide my perspective, and speculate with regard to future directions.

We now know that the majority of PAH patients with more than 1 affected family member have a mutation in the gene BMPR2, which codes for bone morphogenetic receptor protein 2, a cell surface receptor of the transforming growth factor (TGF-β) superfamily. Rarely, familial PAH cases may be caused by mutations in genes that code for 2 other cell surface receptors of the TGF-β superfamily, activin-like kinase-type I (ALK-1) and endoglin (ENG), which are associated with hereditary hemorrhagic telangiectasia. There may be other genes, as yet unidentified, that cause PAH.

We also know that BMPR2 mutations can be identified in approximately 1 of every 5 individuals diagnosed with idiopathic PAH. In some instances, these mutations are *de novo* (spontaneous), and in other cases a parent carried the mutation (obligate carrier) without developing PAH (incomplete penetrance). The presence of mutations that cause disease in individuals diagnosed with idiopathic PAH (IPAH) necessitated a change in diagnostic nomenclature. Heritable PAH (HPAH) includes individuals with disease-causing mutations (BMPR2, ALK-1, ENG) and individuals with other family members diagnosed with PAH. The rationale for this change in nomenclature is the fact that either the presence of a disease-causing mutation or a clear family history of PAH identifies an increased risk for other family members to develop PAH.

At the time of the 4th World Symposium, investigators had described 298 BMPR2 mutations. The consensus summary lists the BMPR2 mutations that have been associated with PAH, most of which are unique to each family and are presumed to result in loss of BMPR2 function. Mutations associated with PAH alone are insufficient to cause PAH, as evidenced by mutation carriers unaffected by PAH. The uneven gender ratio of at least 1.7 women affected for every affected man suggests that hormonal factors (genetic and/or environmental) may influence disease penetrance.

Heritable and idiopathic pulmonary arterial hypertension have a similar clinical course, although HPAH may be associated with a younger age at disease onset and more severe hemodynamic impairment at diagnosis. Patients with PAH and disease-causing BMPR2 mutations are less likely to respond to acute vasodilator testing during right heart catheterization and are unlikely to benefit from calcium channel blocker monotherapy. This observation fits the known role of TGF-β receptors such as cytokine growth factors, which control proliferation, migration, differentiation, apoptosis, and extracellular matrix deposition and the concept that dysregulated cellular proliferation underlies HPAH.

Clinical genetic testing is available for BMPR2, ALK-1, and ENG mutations. Genetic testing may be offered to any individual with a family history of PAH or IPAH (without other known affected family members) with the current cost of testing ranging from approximately $1000 to $3000 USD to analyze the affected individual. Testing family members of a patient affected with PAH for whom the exact mutation is known costs approximately $300 to $500 USD. Genetic testing should involve pre-and post-test counselling by a genetic counsellor who understands heritable pulmonary hypertension and the potential psychosocial impacts of genetic test results.
Due to the incomplete penetrance and variable age of onset, identification of a BMPR2 mutation may have a complex and serious psychosocial impact on the family, often associated with guilt in the parent who has passed on mutations to the children. Genetic testing is most helpful when it is able to identify members of the family who are not at risk for PAH and therefore can forgo screening for PAH. The most common reason that individuals pursue genetic testing involves issues of informing their children of their hereditary predisposition or in making informed decisions about family planning. In the past, many patients have failed to pursue genetic testing due to anxiety regarding genetic discrimination. Recognition of these concerns has led a number of countries to introduce either voluntary or legal codes to protect individuals requesting genetic counselling and formal testing. For example, in the United States, the Genetic Information Non-Discrimination Act, passed in May 2008, provides protection from discrimination in coverage or cost of health insurance coverage to members of both individual and group health insurance plans and protects against discrimination in employment based upon a genetic predisposition. Genetic testing of children should be performed with caution due to the potentially significant psychological impact on a child, particularly in the face of overt anxiety for the future development of a potentially fatal disease without methods for effective disease prevention.

**Perspectives**

In spite of dramatic breakthroughs, advances in genetic and genomic understanding of PAH are in the very early stages. Opportunities exist to advance our understanding of the basic molecular pathogenesis of HPAH, to discover new genes and pathways that modify the pathobiology of PAH, and to identify genes responsible for variations in therapeutic response among PAH patients. In the future, collaborative studies of BMPR2 mutation carriers should enable identification of environmental modifiers, biomarkers for disease development and disease progression, and surrogate markers for efficacy endpoints in clinical drug development. With advances in genomic technology and with international collaborative efforts, genome-wide association studies may be conducted to identify genetic modifiers for BMPR2 penetrance and genetic susceptibility to PAH associated with other disorders.

**What critical issues will the genetics and genomics subcommittee address at the 5th World Symposium on Pulmonary Hypertension?**

The answer to this question remains speculative. Based upon goals set at the Dana Point meeting, the committee will undoubtedly examine new scientific observations arising from genetic association studies and confirmed by replication studies. Some key areas for investigation include: (1) understanding difference in gender-specific penetrance; ie, why are women with BMPR2 mutations more likely to develop PAH? Is testosterone protective? Does estrogen or progesterone increase susceptibility? Does autoimmunity play a role? What is the relationship to pregnancy and/or contraceptives?; (2) refined estimates of the penetrance of BMPR2 mutations (studies of familial PAH provide overestimates); and (3) identification of genes that are responsible for the development of other forms of PAH, eg, PAH associated with portal hypertension.

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**Diagnosis and Assessment of Pulmonary Arterial Hypertension: A Glance at the Output From the Dana Point Conference**

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The ideas regarding definition, diagnosis, and assessment of pulmonary arterial hypertension (PAH) are evolving. The importance of objective evaluation of right ventricular (RV) function is now more emphasized. The progress in imaging techniques and biomarkers used to follow patients’ responses to therapy and to screen populations at risk for development of PAH must be monitored and eventually translated into clinical routine. As early treatment becomes an essential target and new therapies are developed, screening, prompt diagnosis, and accurate assessment of disease severity become particularly important. The Dana Point meeting offered a possibility of updating evidence and reaching a consensus regarding its clinical implications in everyday practice.

**Definition of Pulmonary Hypertension**

After some discussion of the threshold of 20 mm Hg as a parameter to define pulmonary hypertension (PH), the consensus decision was to maintain resting mean pulmonary arterial pressure (mPAP) ≥25 mm Hg as a criterion required for the diagnosis of PH. Pulmonary occlusion (wedge) pressure <16 mm Hg at rest is still required before a diagnosis of PAH can be made.

However, based on the evidence provided by Professor Horst Olschewski’s group from Graz (Austria), 2 important remarks were made: the upper limits of normal for mPAP, based on published data, is 20 mm Hg. However, because patients in the 20-24 range of mPAP have not been included in clinical trials, more data...
regarding the natural history in these patients are needed. Importantly, evidence regarding a universal threshold for abnormal exercise mPAP, which would allow an earlier diagnosis of PH induced by a stress test, was considered not conclusive. Exercise hemodynamics were, therefore, removed from the definition of PH.

Noninvasive Definition of Pulmonary Hypertension?

Reliability of noninvasive estimation of pulmonary arterial pressure (PAP) and of PH diagnosis with echocardiography was discussed extensively. Doppler estimates of systolic and particularly mPAP are imprecise in individual patients, although this is despite tricuspid jet velocity (TJV) correlates strongly with systolic PAP and directly measured systolic PAP correlates with mean PAP. This is likely because of the intrinsic limitations of echocardiography and its operator dependency. While it appears reasonable to consider TJV >2.8 m/s and tricuspid insufficiency pressure gradient (TIPG) ≥31 mm Hg at rest as elevated (except in elderly and/or very obese patients), the formal diagnosis of PH and particularly of PAH requires right heart catheterization. Based on current evidence, echocardiography may be used in screening for PAH in mildly symptomatic patients with scleroderma or HIV infection, though relatively high numbers of false positive results and low diagnostic yield are discouraging. Exercise Doppler is not ready for clinical use to improve performance of such screening programs. Healthy volunteers too often display significant increases in TJV and the definition of abnormal echocardiographic response to exercise is still lacking. NT-proBNP (N-terminal pro-B-type natriuretic peptide) seems the most important new candidate for inclusion to echocardiographic screening programs, which should probably also use more comprehensive evaluation of the signs of RV overload instead of limiting measurements to TJVs.

Prognosis and Follow-up

The working group reviewed exciting evidence regarding prognostic markers, as well as the influence of currently available therapies on outcome. Since the meeting in Venice, significant amounts of information regarding humoral biomarkers have been gathered. Data on BNP and particularly on NT-proBNP were considered most convincing. A new prognostically relevant echocardiographic parameter has also been described. It is based on measurement of tricuspid annular plane systolic excursion (TAPSE) toward the apex and represents an easily measurable surrogate of RV ejection fraction. Although elevated NT-proBNP and abnormal TAPSE taken at baseline are predictors of worse survival, it is not clear whether their changes during treatment also have prognostic implications.

Indeed, the working group experts dedicated particular attention to the possibility of monitoring the patients on treatment and optimizing decisions when their treatment should be escalated. Two strategies were reviewed.

The “clinical” strategy is based on the signs and symptoms reported on clinical examination and selected laboratory tests. If functional class (FC) is considered satisfactory and no signs of right heart failure are detected, the therapy remains unchanged. Noninvasive examinations such as echocardiography, biomarkers, and 6-minute walk distance are performed but no prespecified criteria that would prompt a change or escalation of therapy are defined. Usually the intervals between consecutive patients’ evaluations are 3 to 6 months, based on the results of landmark trials that showed poor prognostic significance of maintaining FC III or IV despite 3 months of therapy.

In contrast, the “goal-oriented” strategy of follow up has been proposed to make treatment decisions more objective. Parameters considered prognostically relevant should be kept within predefined “acceptable” limits. Treatment should be escalated until those thresholds are reached. While some encouraging examples from several centers were available, no consensus was reached regarding which parameters should be measured and whether noninvasive evaluation is sufficient in most cases.

Focus on the Right Ventricular Function and Coupling to Pulmonary Arterial System

When discussing parameters potentially useful for follow up, RV function in PAH was found of particular interest. In fact, the usual cause of death in PAH is RV failure. Both diastolic and systolic dysfunction are likely contributors to RV failure. A PAH treatment strategy based on measures that better reflect RV function may be interesting. Cardiac MRI offers an interesting perspective on RV morphology and function. It provides excellent spatial resolution and unrestricted access to any required cross-section of the heart. Cardiac MRI is currently a gold standard in the assessment of cardiac volumes, muscular mass, and ejection fraction of both ventricles. Precise flow measurements in the heart and great vessels can be made using velocity-encoded imaging.

As reported by a Dutch group, baseline RV stroke volume index >26 mL/m², RV end-diastolic volume <83 mL/m², and left ventricular (LV) end-diastolic volume >41 mL/m² indicated better survival and documented further dilatation of the RV. Decreases in LV diastolic volume and/or in RV stroke volume at 1-year follow-up were related to worse long-term outcomes despite treatment. Interobserver variability is low, which makes MRI a potentially useful tool for follow-up assessment; it will remain a research option as long as technical complexity makes it unsuitable for multiple serial testing, which is necessary in routine clinical follow-up of PAH patients.

I believe the best use of data collected from cardiovascular magnetic resonance (CMR) follow-up studies in PAH would involve selecting those parameters which are both indicated as prognostically significant by CMR and are possible to assess with echocardiography. Concentrating efforts on serial assessment of a few well-standardized measurements selected based on their CMR-proven prognostic implications should improve the value of echocardiography in therapeutic decision making in PAH.

Pulsatile hemodynamics represent a relatively unexplored area, accessible in the research setting by high fidelity pressure and flow recordings potentially by CMR, and in clinical practice (to a certain extent) by Doppler echocardiography. Measurements of timing and amplitude of the reflected pressure waves may influence our understanding of the coupling of RV to the pulmonary arterial bed and the efficacy of RV work. Cardiovascular magnetic resonance studies indicate that even the simplest pulsatile parameter such as RV stroke volume seems more prognostically relevant than an averaged cardiac output.

Looking Backward and Forward

I have mixed feelings about the work completed in the area of diagnosis and evaluation of PAH at the meeting in Dana Point. Just before this meeting, some PAH experts were advocating revolutionary changes in the definition of PH and PAH. Lowering the PH definition threshold to 20 mm Hg and creating a well-defined severity level based not only on pressure but also pulmonary vascular resistance had been suggested. After discussions, the work-
ing group supported the conservative positions and limited the changes to the removal of exercise criteria of PH, retaining the simple and universally recognized definition based on resting PAP $\geq 25$ mm Hg. Another area that did not change much despite earlier expectations was the approach to echocardiographic diagnosis of PH. When compared with the Venice consensus, which offered an option of making an echocardiographic diagnosis of "mild PH," we may have even taken a step back. The current document limits the statement to a prudent: "it appears reasonable to consider TJV $>2.8$ m/s and TIPG $\geq 31$ mm Hg at rest as elevated, except in elderly and/or very obese patients." In addition to collecting and digesting new evidence in PAH, the objective of future meetings must involve providing clearer indications about when to proceed to right heart catheterization and when to consider echocardiography as sufficient evidence of PH, particularly in the presence of clear causative factors such as lung or left heart disease. Professor Robert Naeije’s suggestion to create and prospectively validate a noninvasive score assessing the “probability of PAH” and assisting in the decision whether to perform right heart catheterization seems very timely.

New evidence that could be useful in identification of an optimal set of goals to be achieved by PAH therapy would be most welcomed before the next world meeting, which should preferably be dedicated to the entirety of the pulmonary circulation rather than just PH. ■

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**Updated Evidence-Based Treatment Algorithm in Pulmonary Arterial Hypertension**

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Ernst von Romberg, a German physician, described an autopsy in 1891 as “pulmonary vascular sclerosis”; however, only with the introduction of intravenous epoprostenol in 1995 have disease-specific targeted medical therapies for pulmonary arterial hypertension (PAH) become available. Furthermore, significant advances in the treatment of PAH have occurred during the past 15 years, with 8 medical therapies now approved. These agents target the prostacyclin pathway, the nitric oxide (NO) pathway, and the endothelin (ET-1) pathway. In addition, combination trials have demonstrated additive or synergistic benefit by targeting 2 or 3 of these pathways (Figure 1).

At the 4th World Symposium on Pulmonary Hypertension in Dana Point in early 2008, both uncontrolled and controlled clinical trials with different compounds and procedures were reviewed and compared to define

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*Key Words—idiopathic, calcium channel blockers, functional class, atrial septostomy, lung transplantation*

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*Figure 1. Pathways now defined for the treatment of PAH. (reprinted with permission from Humbert M, et al. New Engl J Med. 2004;351:1425-1436).*
the risk-benefit profiles for PAH therapeutic options. The objective of the Medical Treatment Task Force at the Dana Point meeting was to review all the randomized controlled trials (RCTs) performed in PAH and to propose an evidence-based updated treatment algorithm that would incorporate the currently available therapies. These clinical studies included compounds targeting 3 pathways in the pathobiology of PAH; ie, the NO pathway, the ET-1 pathway, and the prostacyclin pathway.

Nineteen RCTs with 8 compounds as monotherapy have been completed to date in PAH patients. In addition, 5 RCTs testing the combination of agents have been completed. Approximately 5000 patients have participated in these studies to date to develop effective treatments for PAH and, ultimately, to find a cure for PAH.

A grading system incorporating both the quality of evidence and the magnitude of the treatment effect was utilized in developing the PAH treatment algorithm (Figure 2). The algorithm included drugs approved by regulatory agencies for the treatment of PAH and/or drugs available on the market for other indications. The different treatments that have been evaluated were studied primarily in idiopathic or heritable PAH, and in PAH associated with connective tissue diseases or with anorexigen use. Extrapolation to the other PAH subgroups should be done with caution.

Oral anticoagulation remains proposed for idiopathic and heritable forms of PAH, whereas diuretic treatment and supplemental oxygen are indicated in cases of fluid retention and hypoxemia, respectively. High doses of calcium channel blockers remain indicated only in the minority of patients who are responders to acute vasoreactivity testing. Nonresponders to acute vasoreactivity testing, or responders who remain NYHA functional class III, should be considered candidates for treatment with either an oral PDE-5I or an oral ERA. Continuous intravenous administration of epoprostenol remains the treatment of choice in NYHA functional class IV patients. Combination therapy is recommended for patients treated with either PDE-5I or ERA monotherapy who remain NYHA functional class III. Both atrial septostomy and lung transplantation are indicated for refractory patients or where medical treatment is unavailable.

The conclusions derived from the clinical trials over the past 15 years will allow us to treat patients with an evidence-based treatment strategy. In addition, we look forward with enthusiasm to reviewing ongoing and future clinical trials in 2013 at the 5th World Symposium on Pulmonary Hypertension in Paris with the next update to follow in evidence-based PAH treatment strategies to further improve outcomes for PAH. ■
Diagnosis, Assessment, and Treatment of Nonpulmonary Arterial Hypertension Pulmonary Hypertension: A Brief Summary From the 4th World Symposium on Pulmonary Hypertension

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The 4th World Symposium in Dana Point was the first among the world meetings on pulmonary hypertension (PH) that assigned a working group to address in detail the so-called nonpulmonary arterial hypertension (PAH) forms of PH; ie, those forms of PH that are seen in patients with chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), left heart disease, venous thromboembolism, and other conditions. The full manuscript from this symposium has been published in July 2009, and this short summary will provide a brief synopsis of the working group’s recommendations.

Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is one of the most common conditions associated with PH. In patients with advanced COPD, PH, defined by a mean pulmonary artery (PA) pressure >20 mm Hg at rest, may be detectable in up to 90% of patients. However, in the vast majority of these cases, PH is relatively mild with mean PA pressures between 20 and 30 mm Hg and a normal cardiac output. Progression of PH is usually slow, especially when these patients are receiving long-term oxygen therapy. Affected patients may present with signs of diastolic right ventricular dysfunction, particularly elevated right ventricular filling pressures and edema. Right heart failure with low cardiac output as seen in PAH is exceedingly rare. Nevertheless, the presence of PH in COPD patients is an ominous prognostic sign since even mild PH is an independent risk factor of mortality in this patient population.

Several authors have described a small subgroup of COPD patients with so-called “out-of-proportion” PH; ie, severe PH with hemodynamic features resembling those seen in PAH. The prevalence of this form of PH ranges from 1% to 5% among COPD patients and there is no relationship between the severity of COPD and the severity of PH.

Few studies have addressed medical treatment of COPD-associated PH. Several years ago, calcium channel blockers and other vasodilators were tried, but these drugs had no beneficial effects and it was found that any vasodilator had the potential to worsen gas exchange in these patients. More recently, small pilot trials studied the effects of novel drugs that have been approved for PAH in COPD-associated PH. The results of these trials, however, were mostly negative. The endothelin receptor antagonist bosentan did not improve exercise capacity and the drug was even associated with a worsening in gas exchange and quality of life. Preliminary data with the phosphodiesterase-5 inhibitor sildenafil suggest the same. So far, no study has addressed the role of medical therapy in patients with “out-of-proportion” PH. All in all, it is obvious that the pathogenesis of COPD-associated PH differs from that of PAH so that the drugs used in PAH may not necessarily be effective in COPD-associated PH.

Pulmonary Hypertension in Interstitial Lung Disease

Pulmonary hypertension is a common complication of ILD and has been associated with clinical worsening as well as a poor prognosis in this patient population. As in COPD, it is unclear if patients with ILD-associated PH may benefit from PH-targeted medical therapy. Short-term improvements have been reported with sildenafil and inhaled iloprost but rigorous studies are lacking. So far there is no sufficient evidence regarding the safety and efficacy of PAH drugs in this patient population and no drug has been approved for the treatment of ILD-associated PH.

Recommendations for the Management of Pulmonary Hypertension in Chronic Obstructive Pulmonary Disease and Interstitial Lung Disease

Echocardiography remains the most important initial diagnostic tool once PH is suspected in chronic lung disease. However, the limitations of echocardiography are well known and false positive as well as false negative findings have been reported. Biomarkers, especially brain natriuretic peptide (BNP), may also have a role in detecting PH in patients with underlying lung disease, but BNP lacks sensitivity (especially for milder forms of PH) and specificity since elevated levels may also reflect left heart disease. Thus, whenever medical therapy of PH is considered, confirmation by right heart catheterization should be sought. The same is true for patients entering clinical trials since it is of utmost importance to characterize those patients who may benefit from PH-targeted therapy.

Regarding medical therapy, the used of the so-called PAH drugs is not yet recommended in patients with COPD or ILD and...
PH as there are no robust data regarding safety and efficacy of any of these drugs in these patient populations. It is evident that some patients with severe PH may benefit from targeted therapy but for now this decision should be left to expert centers.

**Chronic Thromboembolic Pulmonary Hypertension**

Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the most prevalent forms of PH. Chronic thromboembolic pulmonary hypertension differs from PAH by its major vessel involvement of the vascular remodeling process, which can be approached surgically by pulmonary endarterectomy (PEA) as the treatment of choice for this condition. However, small vessel arteriopathy is variably present in CTEPH and the extent of small vessel arteriopathy is an important determinant of the outcome after PEA.

Perfusion scanning remains the examination of choice for ruling out CTEPH. A normal or “low-probability” perfusion scan in a patient with PH effectively rules out CTEPH. Patients with at least 1 segmental or larger perfusion defect should undergo further imaging, including computed tomography of the chest. If PEA is considered, most centers will ask for a pulmonary angiogram, but this examination should be performed at the center where surgery would take place.

There is an ongoing debate whether or not the so-called PAH drugs are efficacious in patients with inoperable CTEPH. While several open-label studies with bosentan, sildenafil, and prostanoids have reported favorable results, the only randomized, controlled trial (BENEFIT, bosentan vs placebo) failed to show improvement in exercise capacity after 16 weeks of therapy. Thus, the working group called for additional studies and did not recommend the general usage of PAH drugs in CTEPH.

**PH Associated With Left Heart Disease**

Left sided heart disease is one of the most common causes of PH and it is seen in patients with systolic heart failure as well as diastolic heart failure. The pathogenesis of PH in left heart disease is complex. There is a passive (pulmonary venous) component in response to increased left atrial pressure. In some patients, a superimposed active component due to pulmonary arterial vasoconstriction and precapillary vascular remodeling may lead to further increase in pulmonary arterial pressure.

In some cases it can be difficult to distinguish between PH due to diastolic left ventricular (LV) dysfunction and PAH. Risk factors of LV dysfunction include an older age, hypertension, obesity, diabetes, and other conditions. Although echocardiography provides important information, invasive measurements of pulmonary capillary wedge pressure or LV end diastolic pressure (LVEDP) may be required to document the presence of elevated LV filling pressures. Occasionally, these pressures are normal at rest so that exercise or volume challenge may be required to unmask LV diastolic dysfunction.

When treating PH in patients with left heart disease the underlying substrate should be the focus of management. So far, there is no indication to use the so-called PAH drugs in this condition as none of these drugs has been thoroughly evaluated in patients with left heart disease.

**Summary**

All of the non-PAH forms of PH have various features that distinguish them from PAH. Differences are seen in the pathogenesis, clinical presentation, diagnostic approach, and response to medical therapy. Medical therapies that have proven effective in PAH have not been sufficiently studied in any other form of PH and further studies are needed to define the role of PH-targeted therapies in these patient populations.

**Members of the non-PAH PH working group:**

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84 Advances in Pulmonary Hypertension
The task presented to the Future Perspectives working group at the 4th World Symposium on Pulmonary Hypertension meeting in Dana Point was daunting: to identify what can be expected in the near future in the treatment of this complex disease process. The topics discussed were varied and highlighted the challenges in translating experimental results into therapies, all the while recognizing that we have not yet achieved the ultimate goal—a cure.

Genetic Variation of Pulmonary Arterial Hypertension
Approaching the genetics of pulmonary arterial hypertension (PAH), the working group reviewed the current status of understanding of multiple pathways already implicated in PAH, including the bone morphogenetic protein receptor 2 gene and the downstream regulators, the Smad proteins. The group reviewed the latest updates regarding types and occurrence of mutations in PAH and hypothesized potential mechanisms of disease related to these mutations, including their central role in cellular proliferation and vascular remodeling. Polymorphisms in the genes that encode endothelin receptors, serotonin pathway members, prosta
cyclin synthase and receptors, and endothelial nitric oxide synthase were also discussed. In all, this section highlighted the current status and the complexity of genetic mutations in the pathogenesis of PAH.

Mutations and polymorphisms in other systems such as G-protein-coupled receptors, potassium channels, naturetic peptides, and the NADPH oxidase system, which have been implicated not only in PAH but also in hypertension and heart failure, were discussed as well. While direct links to PAH therapeutics have not yet been identified, these mechanisms represented new genetic targets to consider in the pathogenesis of disease and potential new targets for treatment.

One of the most important discussions regarding genetics in PAH centered on the evolving field of pharmacogenomics and the potential for personalized PAH therapies. Clearly, pharmacogenomics in PAH is in its infancy, but this discussion highlighted the importance of including genetic analyses in future clinical studies.

Angiogenesis
The committee was very saddened by the unexpected death of Dr Judah Folkman just prior to the Dana Point meeting. He was invited to review this important topic for the working group, as his research has led to many of the seminal findings in angiogenesis, and his absence was deeply felt. The group reviewed the potential role of antiangiogenesis strategies in PAH, including current inhibitors of vascular endothelial growth factor, the tyrosine kinase inhibitors, and other intracellular targets including PI3K/AKT, among others. The following discussion focused on the unresolved questions of the role of angiogenesis in PAH—most importantly, is angiogenesis a friend or foe? While no clear conclusion was drawn regarding the role of angiogenesis, the potential use of these agents in PAH was considered.

Growth Factor Inhibitors
With the understanding that clinical trials of growth factor inhibitors are underway, the working group reviewed the available clinical and preclinical information on PAH. While much of the discussion focused on PDGF, other growth factors were also discussed as viable targets for PAH therapies. Overall, there is broad enthusiasm for growth factors as important therapeutic targets in the near future.

Endothelial Stem/Progenitor Cells
The therapeutic potential of stem/progenitor cells in the treatment of PAH brought the working group up to date with the status of current clinical trials. Importantly, the discussion also considered the potential pathogenic contribution of stem/progenitor cells on the pulmonary circulation in actually precipitating PAH. One significant limitation in this area has been the lack of clear understanding of the localization of administered stem/progenitor cells in the PAH lungs. Molecular imaging techniques may be very useful in long-term “visualization” of therapeutic transgenes.

RV Remodeling
Regardless of the etiology of PAH, the performance of the right ventricle (RV) will ultimately determine patient outcome. Limited therapies specifically target the RV, and the importance of focusing on the right heart (separate from the left ventricle [LV]) was emphasized in both diagnostic evaluation and therapies.

Understanding the fundamental components of the RV workload (including understanding ventricular-vascular coupling) and the hypertrophy/failure response of the cardiac myocyte was reviewed. Much discussion of the pathogenic vs physiologic adaptation of the RV again demonstrated the need to increase understanding of the RV as distinct from the LV as application of LV-derived therapies in heart failure cannot be extrapolated to the RV.

Summary
Overall, the Future Perspectives working group tackled a broad array of topics focusing on identifying seminal areas for ongoing therapeutic development. Like so many of the working groups, the understood goal is ultimately a cure for PAH. Until then, creative, thoughtful approaches to new therapies in PAH are urgently needed. The group certainly felt hopeful that, prior to the next World Symposium, some of the targets discussed will have been tested in the clinical arena.
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Self-Assessment Examination
See answer key on next page

1. Which of the following statements is NOT part of changes implemented to the Dana Point Classification of Pulmonary Hypertension?
   a. The term Heritable PH replaced the term Familial PH
   b. Schistosomiasis is now part of Group I PAH
   c. Hemolytic anemias are reclassified as their own subgroup under Group I PAH
   d. PAH associated with congenital heart disease has been reclassified to Group II PH (left heart disease)
   e. Group IV CTEPH has been simplified with proximal and distal descriptions removed

2. All of the following reflect current understanding of genetics in PAH except:
   a. BMPR2 is a cell surface receptor of the TGF-β
   b. Heritable PAH includes only those individuals whose family members have been identified to carry the mutation in the BMPR2 gene
   c. Other cell surface receptors whose mutations have been implicated in PAH include ALK-1 and endoglin
   d. BMP2 mutations have been identified in about 20% of IPAH patients

3. Which of the following statements is true about heritable PAH (HPAH)?
   a. HPAH is more common among older individuals presenting with newly diagnosed PAH
   b. Patients with HPAH are more likely to respond to acute vasodilator testing and hence increased likelihood of responding to calcium channel blockers
   c. Patients with HPAH are likely to have more severe hemodynamic impairment at the time of diagnosis
   d. Genetic mutations involved in HPAH affect every generation with complete penetrance

4. With regard to diagnosing and assessing prognosis in PAH, which of the statement(s) is/are most correct?
   a. Tricuspid jet velocity >2.8 m/s and tricuspid insufficiency pressure gradient >31 mm Hg at rest are elevated and diagnostic of PAH
   b. Patients who remain FC III or IV after 3 months of therapy portend poor prognosis
   c. The current definition of PAH has excluded exercise hemodynamics due to inconclusive evidence
   d. B and C
   e. All of the above

5. All of the statements are correct with regard to current state of PAH therapies except:
   a. There are currently 8 PAH-specific therapies approved in the US
   b. Oral anticoagulation is recommended for idiopathic PAH and all subgroups of PAH patients in the absence of contraindication
   c. High doses of calcium channel blockers are indicated only in those patients who are responders to acute vasoreactivity testing
   d. Treatment of choice for functional class IV patients remains continuous administration of intravenous epoprostenol
   e. Combination therapy is recommended for patients treated with either PDE5 inhibitors or endothelin receptor antagonist who remain FC III

6. In reference to PH associated with chronic obstructive pulmonary disease (COPD) and interstitial lung disease:
   a. Even mild PH is an independent risk factor of mortality in patients with COPD and PH
   b. Echocardiogram is an effective screening test but has limitations with significant false positive and negative findings in patients with lung disease and PH
   c. No PAH-specific therapies have demonstrated benefit in patients with “out-of-proportion” PH and COPD
   d. A and B
   e. All are correct

7. All of the following statements regarding chronic thromboembolic pulmonary hypertension (CTEPH) are true except:
   a. CTEPH differs from PAH by its major vessel involvement of the vascular remodeling process
   b. CT angiography is the test of choice for ruling out CTEPH
   c. Pulmonary endarterectomy is the treatment of choice for CTEPH for surgically appropriate patients
   d. BENEFIT study is the only randomized, controlled study conducted among patients with inoperable CTEPH

8. In PH associated with left heart disease:
   a. Elevated PA pressures in left heart disease can be due to combination of passive chronic pulmonary venous hypertension and superimposed active component due to pulmonary arterial remodeling
   b. Risk factors for diastolic dysfunction include older age, hypertension, obesity, and diabetes
   c. Invasive measurement of pulmonary capillary wedge pressure or left ventricular end diastolic pressure is necessary to distinguish PH associated with diastolic dysfunction from PAH
   d. B and C
   e. All of the above
4th World Symposium
Project # 406689
Individuals wishing CME credit for this self-study activity should read the text, answer the self-assessment examination questions, complete the form below,* and send by US mail or fax to the following address by September 25, 2010. You should receive a score of 70% or higher for CME credit. Your test will be scored and your participation will be entered into the CME records at the University of Michigan Medical School.

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Your certificate will be mailed within 3 weeks of receipt of request.

Self-Assessment Answer Key

1. a b c d e  6. a b c d e
2. a b c d  7. a b c d
3. a b c d  8. a b c d e
4. a b c d e
5. a b c d e

Name ____________________________ (Please print)
Degree(s) ____________________________
Specialty ____________________________
Street ____________________________
City ____________________________
State __________________ Zip _______
E-mail Address ____________________________
Date Test Completed ____________________________
Check number of CME credits requested
☐ 1.0  ☐ 1.5  ☐ 2.0

* Self-assessment examination may also be completed online at: http://cme.med.umich.edu

Evaluation of CME Activity (see page 76)

<table>
<thead>
<tr>
<th>Poor</th>
<th>Satisfactory</th>
<th>Excellent</th>
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1. Extent to which objectives were met
2. Potential impact on your practice
3. Avoidance of commercial bias or influence
4. Your overall evaluation of this self-study activity

Additional comments about this self-study activity:

Suggestions for future topics:

1. abcde
2. abcde
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88 Advances in Pulmonary Hypertension
A discussion among attendees of the 4th World Symposium on Pulmonary Hypertension took place to share “an insider’s look” into the current and future research and treatment implications in pulmonary hypertension. Myung H. Park, MD, guest editor of this issue of Advances in Pulmonary Hypertension, Assistant Professor of Medicine and Director, Pulmonary Vascular Diseases Program, Division of Cardiology, University of Maryland School of Medicine, Baltimore, moderated the discussion. Participants included Robyn Barst, MD, Professor Emerita, Columbia University, New York; Marc Humbert, MD, PhD, Universite Paris-Sud, French Referal Center for Pulmonary Hypertension, Hopital Antoine-Beclere, Assistance Publique Hopitaux de Paris, Clamart, France; Ivan Robbins, MD, Associate Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee; and Lewis J. Rubin, MD, Clinical Professor, Department of Medicine, University of California, San Diego.

Dr Park: Thank you all for participating in what I hope will be a stimulating and insightful discussion from the 4th World Symposium on Pulmonary Hypertension at Dana Point. The meeting was composed of 11 scientific working groups reviewing and discussing the most current research and information on pulmonary hypertension (PH). The goals of this discussion are to: (1) gain your perspectives as the key contributors of this meeting; “an insiders’ look,” if you will; (2) learn your thoughts on the progress that has been made in pulmonary arterial hypertension (PAH), specifically focusing on the past 5 years since the Venice symposium; and (3) to gain some insight into the future and the challenges that lie ahead of us. So to start the discussion, can you share your thoughts on our current state of knowledge on the genetics of PH? I know this was the main focus on several different parts of the published reports—understandably so given the tremendous amount of research that has been accomplished in this field. What are the current recommendations regarding the screening process? Specifically, who would you recommend this to and when would such a screen be appropriate? And from a clinical viewpoint, how does one follow these patients once they’re identified? Dr Rubin, maybe you can start the discussion?

Dr Rubin: You know, I think maybe Ivan would be the best one to talk about the genetics.

Dr Robbins: Okay, I’ll say a few words. The classification was changed to reflect our updated understanding of the genetics of PAH and in the Dana Point classification, there’s a new category of heritable disease. This includes the families that have a known mutation as well as patients who were previously felt to be idiopathic, but then were found to have a mutation. And at that point their disease becomes a heritable disease. Then, of course, there are well-described families in whom we have not been able to identify a mutation. With regard to following patients with heritable disease, there are some recommendations for serial echocardiograms in family members at risk, although there are no good data supporting this recommendation. We’ve tried to look for some biomarkers and haven’t been successful.

Dr Barst: I think at this point we do not have specific recommendations based on a consensus. And the recommendations really reflect the clinical investigator and clinician. But the one point I’d like to stress strongly is that I do believe there is a very strong consensus from the PAH community that genetic testing should not be done without prior and ongoing genetic counseling. And I think that really is something that’s very, very important to recommend, that first degree relatives don’t just go obtain genetic studies without really going through counseling with the genetic counselor who has the experience working with a PH center.

Dr Park: So if you’re counseling or discussing this with a patient of yours, what specific advice would you give them as to who this is most appropriate for and where they would go to get this kind of specialized genetic screening?

Dr Barst: There are at least several PAH physicians who have had a focus on the genetics of PH including Vanderbilt, Columbia, and Utah, as well as several other
centers. I think it’s valuable if there is a family followed by another center for that investigator to contact one of the larger centers that specifically has genetic counseling. I think all of these centers have lay information that we’ve always had available for our patients and families. That’s certainly a starting point. It doesn’t mean that the patient or his or her family needs to go to one of those centers, but I think it’s something that can be discussed. As we’ve all seen, there is enormous guilt on both sides of the family. There’s guilt if you’ve given the gene to one of your children and you don’t have the disease, and there’s just as much guilt if you marry someone who has the gene and now your child has the disease and you shouldn’t have married someone with the gene. So it’s really very, very complicated. And it does a disservice to patients just to have genetic testing. Now the one instance when I think it is very valuable is if we have a family where we have identified a mutation and there is a woman who is of childbearing age and the issue comes up with regard to potential for pregnancy. Certainly if she has genetic testing and does not have the mutation and it’s been well demonstrated in her family that the disease is associated with the mutation, to me that’s a valuable use for genetic testing. I’m quite comfortable in that instance saying to this young woman that I believe she can go ahead and plan a family.

**Dr Park:** Certainly for family planning, this would be a very important discussion to have with the PH specialist. If I may move on to the next topic, the other very comprehensive portion of the report covers our current knowledge on the pathogenesis and molecular biology of PH. Can you share your thoughts as to what are the new key pathways that have been identified during the past 5 years? And which of those pathways do you think holds the most promise in being translated into potential new therapies within the next 5 years?

**Dr Rubin:** I think we need to recognize that while we have made advances in our understanding of the pathogenesis of this disease, our understanding remains quite incomplete. There are a lot of abnormalities that have been identified. Which of these is important or central or even contributory to the pathogenesis remains to be determined. One of the ways I think we find this out is with clinical trials that use treatments that target those diseases, those mechanisms. And they help clarify for us the relative contribution, the relative importance of those pathways. Certainly there is a great deal of interest in tyrosine kinase inhibitors. You know growth factor pathway contributions; I think there’s interest, great interest, in that. There is VIP, vasoactive intestinal peptide. There is interest in that, and a clinical trial is underway that will help, I think, to clarify that potential role. But we have a lot of potential pathways and we still don’t have a full understanding of the disease mechanism. We’ll need to prioritize for clinical trials which of those pathways have the strongest rationale and the best evidence to go after at this point because our opportunities to study patients in clinical trials are somewhat limited.

**Dr Park:** Thank you, Dr Rubin. Certainly a number of interesting potential targets for new therapies exist. Dr Humbert, any additional thoughts?

**Dr Humbert:** The first thing we can say is that we still have no cure for the disease, but we understand better how to use the treatments targeting endothelial cell dysfunction. We still have a lot of work to select novel pathways which should be targeted in priority. It is widely accepted currently that growth factors such as PDGF or VEGF may be of interest, and we will soon test growth factor inhibitors, which may have a positive action on pulmonary artery remodeling. In addition, genetics may help us identifying additional pathways of interest within the transforming growth factor superfamily. However, despite the fact that we understand more and more the complex pathways involved in heritable and idiopathic PAH, we still don’t know really what should be the target to select in order to prevent or to reverse pulmonary vascular remodeling. Maybe we should emphasize the fact that pulmonary vascular remodeling is extreme in PAH and, when the patients are symptomatic, the vessels are really markedly remodeled. Maybe we should have better tools to identify as early as possible remodeling in patients with predisposing conditions such as systemic sclerosis or genetic risk factors in order to intervene earlier. But this is still science fiction. We don’t have any clue to say that early intervention will translate into reversal of the condition.

**Dr Barst:** I think Marc brings up something that’s very valuable in that it’s a potential prospective study or trial that could be considered. I’m not saying that this is being done or should be, but it’s an area where perhaps we really could investigate, prospectively, patients that are at increased risk to develop the phenotype, that is obligate carriers in families in whom we have demonstrated a mutation. If we identify a cohort of carriers who, in fact, are truly asymptomatic with normal oxygen consumption and normal ventilatory efficiency and normal hemodynamics at rest and with exercise, could we consider a randomized clinical trial evaluating the safety and efficacy of a given PAH therapy in a cohort of asymptomatic obligate carriers? However, it would have to be quite a long study. This is certainly something very premature, but it’s a possible avenue to allow us to explore whether we could prevent the development of PAH. So I think what Marc brings up is very, very valuable. What do we know about early treatment? We do know that at least now we have data from a 6-month randomized controlled trial with only functional class II patients that demonstrated that early intervention seems to be clinically significant from a hemodynamic standpoint and with respect to morbidity and mortality, defined time to clinical worsening. The question I’m intrigued by that Marc brought up: is there some way that we could absolutely prevent the disease from starting?

**Dr Robbins:** We’ve talked about a prevention study in familial disease. I know you have considered that as well, Robyn. The problem is the numbers of patients you’re going to need and the fact that only 20% of obligate carriers are going to get the disease on average.

**Dr Barst:** Absolutely. It’s a consideration. This would have to be an international study.

**Dr Robbins:** Right, and over many years.

**Dr Barst:** Is there some other way from a novel investigative stand-
point where we could see if we can prevent the disease, which is something we all would be most interested in.

Dr Robbins: Well, the scleroderma population may be another group that can be studied prospectively.

Dr Rubin: Right. And that study is actually going to be done, I think, where an at-risk population, scleroderma, with early evidence of disease like exercise abnormalities or no evidence of pulmonary vascular disease will have intervention and look at that vs placebo and the time course of disease development. That also suffers from requiring large numbers because even an at-risk population of scleroderma patients has relatively low incidence of disease development. And Marc and his colleagues, I think, have provided important data in that regard. It also means following patients for long periods of time. But I think it’s an at-risk population that’s probably larger than the genetic population.

Dr Park: I think that provides an excellent segue. One of the topics that received a lot of attention throughout the World Symposium was the importance of early and accurate diagnosis of PH. Certainly, with the increasing number of approved therapies and studies demonstrating that early initiation of treatment is beneficial, the challenge facing us is how can we better diagnose this disease early in the hopes of having a bigger impact? There has also been a lot of discussion on the rationale, usefulness, and possible pathologic mechanism in performing exercise right heart catheterization. And perhaps this may be a way of identifying PAH in the early stage. So in this regard, can the panel comment on the rationale and the science behind taking this portion out of the current definition of PAH? And is the concept of exercise-induced PAH still felt to be clinically important?

Dr Barst: I think it’s important to realize that when we make recommendations and we want to publish consensus guidelines we want these to be applicable to physicians worldwide. We’re not making these recommendations or guidelines for PAH centers. In my opinion, the reason for removing the exercise portion of the definition is not that I don’t believe there is exercise-induced PAH. But if the exercise study is not done in a lab that is well-equipped with experience in performing exercise studies in PH patients, there may be difficulty in obtaining left-sided filling pressures at the time of exercise. My concern was that we may be diagnosing patients who have predominantly left ventricular diastolic dysfunction because an inaccurate or an unobtainable wedge pressure or LVED pressure is not being obtained at the same time that the pulmonary pressure is being obtained with exercise. This does not mean that the condition doesn’t exist. But the concern is to falsely make the diagnosis of PAH when in fact the diagnosis is left ventricular diastolic dysfunction or another disorder which should be treated entirely differently than PAH. If I could take a second to mention another point that I thought you were going to bring up: that’s how critical it is for clinicians to not merely depend upon Doppler-defined PH with suspecting PH because an increased tricuspid velocity regurgitant jet is measured. Without doing confirmatory right heart catheterization we may be significantly overestimating the number of patients that have PH. I think we’re doing these patients a terrible disservice to say we believe you have PH; we will initiate this therapy without having a confirmatory right heart catheterization as part of the appropriate work up before we initiate therapy.

Dr Park: Definitely, I believe we all acknowledge the importance of recognizing the usefulness and the pitfalls of Doppler echocardiography, a subject which was very well discussed in the diagnostic portion of the World Symposium reports. And the important message that diagnosis requires right heart catheterization prior to initiation of treatment was indeed stressed, a critical message which hopefully will reach all physicians who see and treat patients with PAH.

Dr Rubin: Yes, I would just follow up on what Robyn said regarding exercise. I think the message is in part that it needs to be done correctly. But it’s also not just to diagnose PAH. If you can diagnose and unmask diastolic dysfunction of the left heart with exercise causing PH, that’s very useful as well. So exercise testing can be provocative in terms of PH in general. And the important challenge for the physician is, number 1, to reliably perform the test following appropriate standards and quality; and, number 2, to utilize the information to make the correct diagnosis and establish the etiology.

Dr Humbert: It’s indeed very important. Lewis, you just mentioned the Itinérair-Scleroderma study, an incidence study following more than 300 scleroderma patients during 3 years. We performed a screening with Doppler echocardiography for PH in this population and identified 16 patients with PH and no pulmonary fibrosis. Of note, half of the screened patients had PAH and half had left diastolic dysfunction with postcapillary PH. So indeed, echocardiogram was of major interest, but, as you all said, right heart catheterization allowed to properly define who had PAH and who had diastolic left heart dysfunction. Echo is a great tool to screen for patients at risk of PH, but one should not stop investigating patients at this stage. Patients at risk of PAH should have right heart catheterization before being considered for PAH treatment.

Dr Park: With those wonderful comments, I’m going to open up the Pandora’s box of a topic that appears in every major discussion, which is this class of “out of proportion” PH. One of the most novel sections that came out of this meeting was the one devoted to the non-PAH PH, where there is a formalized discussion and proposed recommendations for working up these patients that we see every day in clinical practice. These include patients with left-sided heart disorders and pulmonary disease. I guess my question is: given our current state of knowledge, is there enough evidence that some of these patients may benefit from treatment, thus there may be a rational basis in select patient populations to consider studying them in a systematic way? Do you foresee such a trial in our future in the next 5 years?

Dr Rubin: There’s certainly a rationale to study them in the real world. I think there is experience in treating them. But, of course, in the real world that experience will be mixed. It is certainly a group that in its sheer size, I think, overshadows the other condi-
tions that we see, the true PAH. So there need to be good studies for those patients. And there have been a few small studies. There is a big ongoing study now looking at phosphodiesterase inhibitors in PH due to diastolic dysfunction. I think there is certainly a rationale for studying the many overlapping conditions or mixed conditions.

Dr Robbins: Lew, I think one of the big issues, and I don’t know what the entry criteria were for that study, but is that you have strict entry criteria. In other words, these patients with diastolic dysfunction or left heart dysfunction, are they optimally diuresed? Are they optimally afterload reduced? That seems to be a very difficult thing to sort out. I’m interested to know the criteria they’re using in this study.

Dr Rubin: I don’t know that, per se. But I do know that at least part of the criteria were to optimally diurese them. As far as afterload reduction, I’m not sure what optimal afterload reduction for diastolic dysfunction is. I wish I did know, but I certainly agree that optimal diuresis is a critical element and I believe that’s part of the criteria for the ongoing study.

Dr Park: What I believe we are seeing in the community is a sense of understanding that we already have the evidence of efficacy regarding a certain class of drug in the non-PAH PH patient population. With this line of practice, there is significant potential to do harm, not only from the possible side effects, but also that other, more traditional therapies get overlooked. What would you all consider are best ways to get the right messages out in the community? And to educate our peers?

Dr Rubin: I think we do advocate for education. Those of us on the phone and many of our colleagues spend a good deal of our time and energy lecturing, writing, and encouraging referral to physicians with expertise. Certainly at the patient level there are national and international associations that serve as a resource for education information. The real challenge, I think, is you know we could spend our entire lives lecturing and writing, but if the physicians don’t attend or read then they will not gain that knowledge.

Dr Park: That is so true. Dr Barst, any other thoughts regarding the non-PAH PH patient population?

Dr Barst: No. I think what’s been said was covered well. However, I’d like to make one comment going back to what we were talking about with regard to exercise to emphasize its importance. It’s imperative that if the clinician has any concern of LV diastolic dysfunction in the differential diagnosis, and he is not performing the cardiac catheterization personally, he must speak with the physician who is doing the procedure. More often than not, these patients undergo catheterization after an overnight fast. If it is not performed early in the day, the patient may be somewhat dry with a wedge pressure that’s recorded at 15 mm Hg or thereabout. However, if we were to do provocative testing to rule out LV diastolic dysfunction, we may immediately see an abrupt increase in the wedge pressure that would confirm the diagnosis of LV diastolic dysfunction. It’s very unfortunate for a patient to have a procedure and at the end of the procedure for the clinician to be left with an inconclusive “I don’t know if you have LV diastolic dysfunction or not until we re-evaluate you.”

Dr Humbert: Maybe one comment about COPD and chronic respiratory disease. In this rather large population of patients, it is appropriate just to emphasize again that echocardiography is not easy and most of the patients with PH have difficult echocardiograms. When there is a question about possible severe PH in these populations. It’s recommended to perform once again a right heart catheterization. The word “disproportionate” is difficult to define but when the patient has a mean PAP above 35 to 40 mm Hg they usually correspond to a very unusual population even though they have significant COPD. So in COPD, first echocardiography might be difficult to interpret. And second, severe PH is rather rare and when present it should be considered as unusual and investigated because many of these patients have another cause of PH such as chronic thromboembolic PH or left heart disease. So these patients are difficult to study and when one investigates them, all possible causes of PH should be considered, even in the setting of established COPD.

Dr Robbins: The other thing, Marc, is that some of these patients have been referred to our center when an echocardiogram was obtained in the hospital during an acute exacerbation when they’re much more hypoxic. As we all know hypoxia is a very potent stimulus for increasing pulmonary vascular pressure. So I think I agree with you there are a lot of caveats in trying to study and treat these patients.

Dr Rubin: You’re right. You’re right. COPD patients with exacerbations should be stable when investigated. If we consider treating these patients with PAH therapy, there is room for studies. For the moment there is no approval in this population.

Dr Park: Again, thank you for leading the discussion with another natural segue. In comparing the most recent treatment guideline from this World Symposium to the previous one, what would you consider to be the most significant changes? And now I am asking to gain an insider’s point of view: what were some of the contentious points during discussion and what were some of the topics that needed to be ironed out? May I start with you, Dr Barst?

Dr Barst: Sure. I think one of the significant changes between these evidence-based treatment guidelines and those we published from the Venice 2003 meeting are that in 2003 we speculated that combination therapy could be safe and increase efficacy in treating patients who had an inadequate response to PAH disease-specific targeted monotherapy. But we didn’t have the data at that time to support our hypothesis. However, over the

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past 5 years there have been at least several studies supporting the use of combining at least 2 of the 3 approved classes of drugs to increase efficacy in an apparent safe manner. The largest of these studies was the PACES-1 study (Simonneau et al, 2009; Annals of Internal Medicine) in which we evaluated the addition of sildenafil or placebo to patients who were on a chronic stable dose of intravenous epoprostenol therapy. And in addition to seeing improved exercise capacity in the sildenafil-treated patients, although it wasn’t one of the prespecified end points, it was quite interesting to note that there were only 7 deaths in the study and they were all in the placebo group. These data demonstrate that combining a prostacyclin analog, which in this case was epoprostenol, with a PDE-5 inhibitor, which in this case was sildenafil, is safe and can increase efficacy in patients who remain limited on monotherapy alone. There have been at least several other combination studies and perhaps Lew might want to comment on those. We now have strong data to demonstrate that we should consider combining drugs. It’s particularly important—since all the drugs have side effects and many of the drugs are extremely costly—that we know the advantages and disadvantages of monotherapy vs various combinations. And unfortunately why one patient may respond favorably to a given combination and another patient who appears virtually identical to the first patient does not respond remains unclear. This is an area of intense research.

Dr Rubin: I would certainly agree with that. I think the other key additions to the algorithm are new drugs. They’re all in the same families, the same classes of drugs as previous algorithms, but there are some new additions to the algorithm in each of the 3 major pathways. There is also emerging evidence supporting combination therapy, although still a great deal is unknown as far as what the optimal end points are in clinical trials, particularly for combination therapy. Which combinations are particularly robust in terms of efficacy? Which pathways are more important to target for which patients? More severe? Less severe? And then whether starting with a combination vs an add-on design or add-on approach is superior to starting with a single agent? So there are a lot of questions still unaddressed that will be addressed, I think, going forward. We’ll also have new insights and information on drugs that target novel pathways. I think that will be a major advance going forward as well. Of course, there were other additions to the algorithm including rehabilitation and exercise as things that were encouraged. From a patient standpoint, that’s very important. One of the common questions I get asked is, is it bad for me? Is it harmful for me to be physically active? And I think we have fairly compelling evidence now that quite the opposite is the case.

Dr Robbins: Although we have combination therapy data now, what we still need—the one combination that we don’t have—is with combination oral therapies. There are studies ongoing to look at this, but clearly that’s something that many physicians in the community do use, combining a PDE-5 inhibitor and an ERA. And as yet, you know we don’t have conclusive data on that.

Dr Humbert: I agree that all these combination therapies are extremely interesting and, in fact, we are becoming more and more ambitious which is good news. I think another very important addition in the recent guidelines, and we mentioned it a few minutes ago, is early treatment. We now recommend treating symptomatic PAH as soon as it’s class II, which was not the case a few years ago. Everybody thought this was important but now we have strong data in favor of early treatment. And regarding combination, we just mentioned that maybe one day the first-line combination will be of interest. We really need to be more and more ambitious toward this population and we need to use as well as possible all the drugs we have in order to produce better data to support the new treatment strategies. In addition, we hope we’ll have new targets to identify and to treat in the next few years.

Dr Park: As the medical therapies advance, do you foresee a greater or lesser role for some of the surgical therapeutic options for our patients? There’s been a lot of discussion regarding how to best utilize some of the surgical options in PH, such as atrial septostomy and lung transplantation. How do we apply these therapeutic modalities at the most appropriate time to obtain the most benefit?

Dr Hum: Regarding transplantation, this is a very important tool for PH treatment. We need to identify as early as possible the best candidates for lung transplantation because there is still a shortage of lung donors. And obviously there is some subset of the disease like pulmonary veno-occlusive disease that is responding poorly to all available therapies right now. There are also are those patients who are refractory to first-line treatment and second-line combinations. I think the most important nonmedical approach for these patients is, of course, lung transplantation. In the future we need to better identify early those patients who have a poor prognosis and who should be listed on the transplant list before being unstable.

Dr Park: Thank you and, as a closing topic, I would like to ask from the panel, some thoughts regarding future considerations. So looking ahead and putting ourselves in the next 5 years to the 5th World Symposium, what do you foresee as possible changes that we can look forward to and the controversies that lie ahead? And some of the big hurdles that you all envision we have to overcome?

Dr Barst: I think what we should anticipate will be derived from the scientific advancements that Lew and Marc discussed earlier, particularly looking at growth factors and the role of inappropriate programmed cell death. At the same time I would like to caution that if phase II studies demonstrate proof of concept with a given novel compound such as a tyrosine kinase inhibitor, it is premature for a clinician to look at proof of concept data and treat PAH patients off label. It’s exceedingly important, since all of these drugs have significant adverse events. These drugs may have cardiotoxicity and should not be used until we have truly demonstrated with pivotal trials that are well designed and well carried out that a drug is safe and efficacious in the patient population that we are treating. We recently prematurely terminated a clinical study in PH patients with sickle cell disease due to safety concerns. The study and the patient group is not what is relevant to this discussion but what is relevant is that a drug was being eval-
uated that was thought to be safe and efficacious but the trial was stopped by the data safety monitoring board. I would just like to caution physicians not to look at small series of open, uncontrolled data and decide to treat a patient with a drug before it has undergone rigorous study.

**Dr Park:** That is definitely very sound advice for all of us. It is so enticing to think that you know that if you can only add this 1 drug, your patient will get better. Of course, we don’t have enough evidence to say this and this does not always turn out to be true.

**Dr Robbins:** There remain challenges here that have been challenges throughout our attempts to treat this disease. One major issue is that PAH is a rare disease. The patients are limited, and I think the pool of patients to be used in studies is getting fewer and fewer, and the studies likely getting diluted out with more and more marginal candidates. So it’s really becoming difficult to get patients to test these drugs with. In addition, we don’t have a good animal model to even look at the pathogenesis and, as we alluded to earlier on, we see these patients when they all have end-stage disease. All of the pathological changes that we see are end-stage. So we don’t know what the early changes are in this disease. We also don’t know whether the mediator abnormalities that have been reported are the cause or the effect of this disease. So I think those challenges to improving treatment remain. Despite these limitation, as we’ve also talked about, there will be new classes of drugs out there, that will target different abnormalities. And hopefully investigators will think a little more outside the box to target more novel pathways. So that’s where I see it in the next 5 years.

**Dr Rubin:** I agree with that. I think in the next 5 years we’ll certainly get more interesting information on basic pathobiology of the lung vasculature and I think the challenge then will be separating the wheat from the chaff and deciding which are not important and which are upstream and which are downstream mechanistically or just unrelated. As far as therapy goes, I think our big challenge will be to triage, to prioritize the treatments and the studies to provide the strongest quality data that will be clinically meaningful. Because we need to study a homogeneous population and, as Ivan mentioned, I think it has become a bit heterogeneous as trials have been broadened to include countries and centers where there is less experience with the disease and with performance of clinical trials. That has the potential to undermine the validity and the meaningfulness of those studies. So we need collectively, I think, to prioritize and we need to collaborate with industry and with government sponsors to do the studies that are the most important to address the most important questions for us and for our patients and find ways to accomplish that while still meeting their objectives.

**Dr Park:** A Herculean task for sure. Dr Humbert, any final thoughts?

**Dr Humbert:** I think it’s clear that we have to be both original and creative but not take too many risks. For example, when we target growth factor and angiogenesis we don’t really know if angiogenesis is harmful or protective or both. We don’t really know the targets we should prioritize and there are many targets and many combinations of targets. We don’t really know the side effect profile of the novel agents we will use in a population with a cardiovascular condition. So I really agree with all the panel that we have to first identify the best targets based on good quality preclinical and early stage studies and then we have to agree on the targets/pathways and drugs which seem to be the best. But this is challenging because there are currently many, many agents, many pathways, and we really need to be well organized and identify the priorities.

**Dr Park:** Well thank you all so much for taking the time to participate in this roundtable. I think our readers will truly gain some wonderful insights from this discussion. Hopefully we can look forward to more stimulating and challenging topics from the next World Symposium!
What is the current status regarding exercise-induced pulmonary hypertension (PH)?

Nothing in the field of PH generates as much discussion or remains so controversial as the question, “What do you think about exercise-induced PH?” The reason is that, clinically, this is a very relevant question in PH. It may arise in a patient who presents with dyspnea with activity. Echocardiography shows essentially normal pulmonary artery systolic pressure (PASP) at rest and pulmonary function tests are also unrevealing. However, the patient describes ongoing and progressive limitations of activity and tells you that the symptoms are only present with exercise. You perform the 6-minute walk distance, which is not normal. This leads to an inquiry regarding whether patients should be evaluated for pulmonary arterial pressure (PAP) response to exercise.

How to define or assess exercise-induced PH is unclear. This subject was the focus of intense discussion at the recent World Symposium in Dana Point. The working definition of pulmonary arterial hypertension (PAH) previously included an exercise component, specifically mean PAP (mPAP) ≥25 mm Hg at rest or 30 mm Hg with exercise with normal left sided filling pressures (pulmonary capillary wedge pressure ≤15 mm Hg) and elevated post-void residual (>3 Wood units). However, after reviewing available evidence, it was recognized that there was no standardized agreement as to how to define exercise-induced PH. Therefore, the exercise portion of the definition of PAH has been removed.

A systematic review of published data revealed that a significant age-related difference in response to exercise is present. While there were only minor differences in PAP at rest, during slight (HR 100-110 bpm) and submaximal (HR 130-135 bpm) exercise, mPAP was significantly higher in older patients (>50 years of age). The upper limit of normal with slight exercise was 29 mm Hg for people <30 years of age, 30 mm Hg for those 30 to 50 years of age, and 45 mm Hg for people >50 years of age. During submaximal exercise, the upper limit of normal was 33 mm Hg for subjects <30 years of age, 36 mm Hg for those between 30-50 years of age, and 47 mm Hg for subjects >50 years of age. Degree of physical training has also been shown to affect PAPs with exercise. Using supine bicycle in 40 healthy patients, 26 who were highly conditioned athletes, the athletes had a higher PASP with exercise than other volunteers (~50 mm Hg vs <30 mm Hg); this difference is due in part to the higher stroke volume among the athletic cohort. In a large series of patients undergoing advanced cardiopulmonary exercise testing for unexplained dyspnea on exertion, the group at Massachusetts General Hospital described distinct patterns of ventilator equivalents and PAP responses to maximal exercise.

Currently, there is no consensus on how to best evaluate for exercise-induced PH. There have been many studies which have used Doppler echocardiography to assess PAP response to exercise. Although readily available and convenient, exercise echocardiogram has several limitations: inability to measure left sided filling pressures (to evaluate for diastolic dysfunction with activity) and cardiac output (high output failure, increase in PASP due to increase in stroke volume), as well as limitations due to poor acoustic window in some patients.

Thus, right heart catheterization with exercise appears necessary for accurate assessment of PAPs in response to activity, of which no agreement exists on the best method. Some clinicians utilize arm exercise with saline bags as weights, most commonly used when femoral access is utilized for right heart catheterization. This approach has limitations due to movement artifacts that could interfere with pressure tracings and difficulty in obtaining sufficient exercise using upper limbs alone. Others have used bicycle with PA catheters placed via internal jugular; this has the potential to produce most reliable results since obtaining PAPs, wedge pressure (immediately upon cessation of activity), and mixed venous and/or cardiac output can be performed. Some investigatoes use the bicycles in supine position while others use upright ones.

The other unknown factor is if exercise-induced PH should be considered for patients who are at high risk for PAH (family history, setting of associated conditions such as connective tissue disease) with no other explanation for symptoms of dyspnea. Recently, Steen et al published finings in 54 scleroderma patients who underwent exercise echocardiography confirmed by right heart catheterization and determined that exercise studies may be a good method of diagnosing PH early in the high-risk population.

The experts at the Dana Point meeting, based on these data, concluded that further, long-term studies are needed before we can reach any specific conclusions regarding the clinical significance and need for treatment of exercise-induced PH.

References

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What role does cardiac magnetic resonance imaging (cMRI) have in managing pulmonary arterial hypertension (PAH) patients?

The key determinant of survival in PAH is right ventricular (RV) function. Mortality in PAH is not caused by the elevated pulmonary artery pressures per se but by the resultant RV dysfunction and failure. The RV is designed to perform in a low resistance system; ie, the normal pulmonary vasculature. When the RV has to pump the stroke volume against the elevated resistance in PAH, an initial adaptive response occurs in the form of myocardial hypertrophy. Enlargement soon follows in a further compensatory effort of the RV to maintain stroke volume by increasing preload. However, decrease in contractility results in clinical evidence of right heart failure manifested by elevated filling pressures, ascites, and low cardiac output.1

The importance of RV functional parameters in determining survival was recognized early from the results of the Primary Pulmonary Hypertension Registry Study.2 The hemodynamic indices associated with worse outcome were increased right atrial pressure (>12 mm Hg), reduced cardiac index (<2.0 L/min/m²), and elevated mean pulmonary arterial pressure (>55 mm Hg). The first 2 parameters, which reflect functional capability of the RV, have been validated in other studies over the years as reliable hemodynamic markers with excellent correlation to outcome.

However, as stated in the recent National Heart, Lung and Blood Institute RV Working Group report, the “…knowledge about the role of the right ventricle in health and disease historically has lagged behind that of the left ventricle …. The right ventricle has generally been considered a mere bystander, a victim of pathological processes affecting the cardiovascular system.”¹

This “lag” may be due in part to the difficulty in imaging and quantifying the RV structure and function with Doppler echocardiography. The complex geometry of the RV, its thin-walled structure, as well as its interdependent relationship with the left ventricle (LV) makes the chamber challenging to obtain reliable and reproducible measurements with echocardiography.

As stated, RV function and response to treatment are the most clinically relevant parameters to follow in PAH. Although invasive hemodynamic parameters are considered the “gold standard” for the initial diagnosis and assessing response to treatment, it is not always feasible to obtain repeated invasive measurements to follow response to treatment. Thus, growing interest is emerging in the use of cMRI in PAH, due to its high spatial resolution, accurate assessment of chamber size and function (especially the RV), and the absence of acoustic “window” limitations. Disadvantages to cMRI include lack of widespread availability, higher cost, difficulty in assessing unstable patients or those on CADD pumps, and presence of claustrophobia.

The possible uses of cMRI in PAH are promising and include accurate assessment of RV volume and mass, estimation of hemodynamics utilizing curvature ratio and PA flow velocity area, as well as a marker of remodeling with treatment. In a study of 64 patients, cMRI was compared to other conventional tests as a marker of prognosis. At baseline, predictors of mortality included conventional assessments (functional class, hemodynamics, 6-minute walk distance) and RV and LV end diastolic volume dimensions.3 At 1-year follow-up, however, only changes in cMRI parameters of RV and LV dimensions indicating progressive RV dilatation remained significant prognostic factors. The recently completed COMPASS-3 trial evaluated, in 100 PAH patients, cMRI at baseline and after 16 weeks of treatment, along with echocardiography and invasive hemodynamics. The forthcoming results will hopefully provide the necessary information on the future use of this imaging modality. cMRI holds promise as a non-invasive tool to assess for evidence of RV response and remodeling with treatment.

References

This interesting and important article examines the outcomes and characteristics of pulmonary arterial hypertension (PAH) associated with connective tissue disease (CTD-PAH) in the modern era treated in the United Kingdom. Historically CTD-PAH is believed to have a poor prognosis, but there are few good studies specifically examining this patient population. Because the management of all adult CTD-PAH cases in the UK is centralized to 1 of 5 pulmonary hypertension centers, the authors were able to examine the clinical data in a large number of incident cases over a 5-year time period (2001-2006). The strengths of this paper include the use of right heart catheterization data to make the diagnosis of PAH (lacking in earlier cohort studies), inclusion of only incident cases, robust clinical data, and follow up on a large number (484) of patients. The data set is predominately composed of patients with systemic sclerosis (315, 74%) but also included patients with PAH due to other connective tissue diseases such as systemic lupus erythematosus (SLE) (35, 8%), mixed connective tissue disease (28, 8%), and others in smaller numbers. The analyses are subdivided into those with concomitant respiratory disease (FVC <60% or fibrosis on CT scan) and there is also a group of patients with exercise-induced PAH examined over the course of the study. Some of the interesting observations include 1- and 3-year survival rates for SSc-PAH of 78% and 47% respectively, and a 3-year survival rate of 75% for patients with SLE-PAH (significantly better then those patients diagnosed with SSc-PAH, P=0.01). It is also interesting to note that 19% of the patients with exercise-induced PAH progressed to PAH at rest over the time period of the study, and there was an appreciable mortality even in this group of patients. — TMB


The association of chronic thromboembolic pulmonary hypertension (PH) has been well described in the literature and carries a significant morbidity and mortality. A large number of studies have examined imaging modalities for the diagnosis of acute pulmonary embolism; however, there are few studies that investigate the detection of chronic thromboembolic pulmonary disease (CTEPD). This article is the first to explore the utility of ventilation perfusion (V/Q) scintigraphy vs multidetector CT angiography for detecting CTEPD in a head-to-head fashion.

The authors of the article retrospectively reviewed the results of 500 patients diagnosed with PH that had both a V/Q scan and CTPA performed at Hammersmith Hospital, London. Of the initial 500 patients screened, 227 fulfilled the inclusion criteria. Interpretation of V/Q scintigraphy was made according to modified PI-OPED criteria. Multidetector CTPA performed was suggestive of CTEPD if there was visualization of the thrombus, calcified thrombus, recanalization, sudden change in vessel caliber, strictures, poststenotic dilatation, webs, or perfusion abnormality. Pulmonary DSA was performed on 61 of the 227 patients.

Ninety percent of patients had the V/Q scan and CTPA performed within 10 days of each other, with 73% of both studies within 48 hours. The investigators separated out the participants into 2 groups: Group A, 78 patients with CTEPH; the diagnosis was confirmed in 61 patients with pulmonary digital subtraction angiography (DSA). The remaining 17 patients were either not fit for pulmonary endarterectomy or did not consent. Group B patients were those with non-CTEPH, 149 patients whose clinical and imaging picture did not suggest thromboembolic phenomena, so no DSA was performed.

This small, retrospective study is the first to make a head-to-head comparison of V/Q scintigraphy and CTPA in the evaluation of CTEPD. It showed that V/Q scans have a higher sensitivity and lower specificity then CTPA for detection of clot. It is important to note that the allocation of intermediate V/Q scan patients impacted the results of the V/Q scan groups. When intermediate V/Q scans were grouped along with high probability scans the sensitivity increased by 1.2%, decreased specificity by 4.6%, and decreased positive predictive value (PPV) by 6.8% and had a negligible effect on the negative predictive value (NPV). The authors concluded that grouping the intermediate probability patients with low probability V/Q scans (using only high probability scans as positive scans) would maintain a high sensitivity and NPV improve specificity, PPV. One major limitation of this study is that not all patients enrolled had a DSA for confirmation of pulmonary embolism. Group B patients were thought to have non-CTEPH based upon CT or V/Q scan, and no DSA was used to confirm lack of embolism. In addition, the remaining members of group B (17 patients) did not have a definitive study either, due to inability to consent or patients were not considered suitable candidates for thrombectomy. Lack of DSA in these groups affect

**Section Editors:** Todd M. Bull, MD, FACP, and Francisco Soto, MD, MS

**Summaries and commentaries from the section editors and invited reviewers present a clinical context for practitioners’ application of the latest published research relevant to care of patients with pulmonary hypertension.**

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the sensitivity and specificity of V/Q scan in detection of CTEPD. A potential future direction would include a larger scale study in which patients all patients enrolled received DSA, V/Q scan, and CTPA. — TMB


Pulmonary arterial hypertension (PAH) is a major cause of morbidity and mortality in patients with systemic sclerosis (SSc). There is great clinical interest in developing effective means of screening these patients for evidence of PAH in hopes of initiating therapy earlier and perhaps impacting outcomes. In this interesting study by Hagger et al, MRI is examined as a possible screening tool for PAH in patients with SSc. Earlier studies have shown that the MRI measured ventricular mass index (VMI), defined as the ratio of the right and left ventricular diastolic mass, correlate strongly with the mean pulmonary arterial pressure (mPAP). The authors have now examined the utility of the VMI in the SSc spectrum of disease. Forty patients, 28 of whom were diagnosed with PAH at rest, were included in the study. Ventricular mass index was found to be elevated in SSc patients with PAH as compared to those with normal PA pressures (0.89 ± 0.3 vs 0.55 ± 0.1, P<0.001). The VMI correlated strongly with mPAP in these patients (r=0.7). Receiver operating curves were used to identify optimal diagnostic threshold levels for PAH using VMI. The 2-year survival rate for patients with a VMI <0.7 vs ≥0.7 was 91% vs 43%. While intriguing, it is notable that all patients entered in this study were referred for a suspicion of PAH. The findings may be different in an unselected population. It is also notable that the tricuspid gradient as measured by echocardiography also had excellent correlation with mPAP measured at cardiac catheterization. Therefore, echo remains a more appropriate initial tool for screening. Still, there are scenarios where an adequate tricuspid regurgitant jet can not be measured and a previous echo study by Mukerjee et al (*Rheumatology* 2004, 43:461-6) could not identify a lower threshold for a tricuspid gradient that excluded the diagnosis of PAH in patients with SSc. MRI could then be considered as a screening tool in patients where echo was nondiagnostic but suspicion remains high. Further prospective studies should be considered with this rationale.— TMB


There is a great need for novel and useful biomarkers to both assist with diagnosis and track disease progression in patients with pulmonary arterial hypertension (PAH). The authors of this manuscript demonstrate that growth differentiation factor-15 (GDF-15) may play such a role. GDF-15 is a member of the TGF-β cytokine superfamily. Several studies have demonstrated that GDF-15 can be induced in cardiac tissue during pathologic periods of stress such as acute coronary syndrome, chronic left-sided heart failure, and pulmonary embolism. Right ventricular overload has been noted to increase in GDF levels, which led the authors to investigate GDF-15 expression in idiopathic pulmonary arterial hypertension (IPAH).

The authors examined the diagnostic and prognostic utility of GDF-15 in the evaluation of patients with IPAH. This involved the evaluation of a retrospective cohort of 76 patients with IPAH from 1999-2004. A second prospective group included 22 consecutive IPAH patients over a 1-year period with follow-up right heart catheterization at baseline and 3-6 months, during which response to medical therapy was evaluated.

Fifty five percent of patients in the first cohort had elevated GDF-15 levels at presentation. Furthermore, elevated GDF-15 levels are associated with a poor prognosis in patients with IPAH. In the first patient cohort those patients who died (39/76) or underwent transplantation (3/76) had a significantly higher median GDF-15 at baseline compared to those who did not have these adverse events.

Interest in using panels of biomarkers for prognostication or diagnosis in a variety of diseases, including PAH, has arisen recently. GDF-15, in combination with NT-proBNP, identified patients at risk for adverse outcomes (death or transplantation). However, it was not demonstrated to be useful in monitoring response to treatment in this study.

The take-home messages of this study were that GDF-15 might be a novel useful biomarker for predicting outcomes in patients with IPAH. The source of GDF-15 in this patient population remains unclear. — Michael Risbano, MD, Pulmonary Hypertension Fellow, University of Colorado, Denver, and TMB
Clinical Trials Update

Fernando Torres, MD  Deborah Jo Levine, MD

Section Editors: Fernando Torres, MD, and Deborah Jo Levine, MD

We would like to introduce you to a new section in Advances in Pulmonary Hypertension in which we highlight results from ongoing and recent clinical trials.

The preliminary results of several multicenter clinical trials have recently been presented. In this issue, we will focus on the results of Freedom-C, which was presented in November of 2008, as well as the Walk-PHαSST study, which was stopped early in July 2009.

**FREEDOM-C: A 16-Week, International, Multicenter, Double-Blind, Randomized, Placebo-Controlled Comparison of the Efficacy and Safety of Oral UT-15C SR in Combination with an ERA and/or a PDE-5 Inhibitor in Subjects with PAH.**

Oral UT-15C SR is an oral prostacyclin (treprostinil) which is slowly released into the gastrointestinal tract after ingestion. The primary endpoint of this trial was to evaluate how the addition of oral treprostinil affected the 6-minute walk distance (6MWD) in patients with PAH who were already taking an endothelin receptor antagonist (ERA) and/or a phosphodiesterase-5 (PDE-5) inhibitor. Secondary endpoints included time to clinical worsening (TTCW), Borg dyspnea scale, WHO functional class, dyspnea fatigue index, as well as others.

The study enrolled 350 patients. The median change on the 6MWD was only 11 meters at 16 weeks ($p=0.07$). Several secondary endpoints like TTCW ($p=0.46$), WHO FC ($p=0.96$), and Borg score ($p=0.06$) did not achieve statistical significance. The combined 6MWD/Borg dyspnea score ($p=0.01$) and dyspnea fatigue index ($p=0.01$) did, however, reach a statistical difference.

This was the first multicenter trial to include patients on multiple PAH medications. This is important to note as it is believed to be more difficult to show a significant change in 6MWD in patients who are taking baseline PAH medications than in those on no previous medications. Consequently, this study does show promise, as the median increase in 6MWD at 12 weeks was 13 meters ($p=0.015$). A major problem in this trial was the undicted rate at which patients dropped out of the study due to side effects. Headache and gastrointestinal intolerance were the main side effects reported. About 25% of the patients could not tolerate a dose higher than 1 mg twice a day, and 14% of patients eventually discontinued the study medication due to intolerance.

The analysis of the results indicated that the initial dose of study drug was likely too high, which contributed to side effect intolerance and thus an inability to up-titratae the drug. The fact that there was a trend toward improvement in the 6MWD and the fact that the dose could likely be better tolerated if started at a lower dose led United Therapeutics to repeat the trial with a different dosing plan. This new trial is currently enrolling patients.

**Walk-PHαSST Study (NCT00492531): A multicenter, randomized, placebo-controlled clinical trial to test the safety and effectiveness of sildenafil for pulmonary hypertension in patients with sickle cell disease.**

This was a 16-week, NIH-sponsored study looking at the efficacy of sildenafil therapy on exercise capacity. Secondary endpoints included changes in shortness of breath, pain crisis, pneumonia, and increased survival. The patients were randomized to receive sildenafil or placebo for 16 weeks. After that, they had the option of going into the open arm, receiving sildenafil for up to a year.

The study enrolled 76 patients. Unfortunately, after 33 patients had finished the 16-week trial, an interim safety data review showed significantly more episodes of serious adverse events in the treatment arm (38% vs 8% in the placebo arm). The most common complication was sickle cell crisis, requiring admission to the hospital. Therefore, the study was terminated prematurely for patient safety concerns.

**Commentary**

The results of these preliminary trials were somewhat disappointing. Freedom-C would have provided us with the first oral prostacyclin in the United States. In 2003, the lack of efficacy of beraprost was published and the medication was never taken to the FDA for approval. Thus, at this time, we still do not have an oral prostacyclin in the US market.

Walk-PHαSST study was also frustrating for the PH community. Dr. Gladwin has worked tirelessly to explore ways to improve the life of sickle cell patients who develop pulmonary hypertension. This is the second sickle cell disease trial that did not show efficacy. The first one was the ASSETT trial, which was halted early due to lack of enrollment.

Multiple clinical trials are in progress looking at the effects of various medications on pulmonary hypertension. Each issue, we will focus on a few of these trials and add updates to those we have discussed in previous issues. For more information on these trials please refer to:

http://www.nhlbi.nih.gov/
http://www.unither.com/oral-treprostinil-for-pah/
I began working with pulmonary hypertension patients in 1998, when the only FDA-approved drug was Flolan. I am amazed that in a span of 11 years we now have 8 FDA-approved drugs with several more on the horizon. This has been possible only through research coupled with the dedication of subjects willing to participate in research studies, physicians willing to be principal investigators, and allied health staff willing and able to perform the work, monitor the progress, anticipate the problems, and collect the data.

There is a saying that it takes a village to raise a child. It also takes a multidisciplinary team to generate the best research. A RN study coordinator’s job is like working on a puzzle: one must keep track of all the pieces, provide support for others as they complete their portion, and then fit all the pieces together into a successful finished product.

What do RN study coordinators do? They are essential for contributing to all aspects of the project in order to achieve successful completion. Responsibilities include coordinating the process of daily study administration; feasibility evaluation; protocol development; budget and contract negotiation; screening, recruiting, and enrolling participants; consenting, scheduling, testing, data collection, dispensing study drugs, and managing the use of investigational devices; managing and reporting side effects; ensuring accuracy of documentation; maintaining databases; responding to the sponsors’ questions; and providing safety and support for the subjects and their families. All of this must occur while following good clinical practice, institutional policies and procedures, and the regulatory requirements necessary for human subject research. To accomplish these objectives, the ideal study coordinator must be pleasant, flexible, compulsive, detail oriented, and extraordiarily well organized.

The investigator, sponsor, regulatory agencies, and subject rely on the RN study coordinator to carry out the study requirements reliably and with a substantial degree of independence. Thus, communication and collaboration with the principal investigator, other team members, sponsor, monitor, and subject are vital pieces of the puzzle. This relationship grows over time through open and effective exchange of information and the development of trust.

The success of any study depends upon all members of the team fulfilling their roles, but in many ways the RN study coordinator is the most vital component of all. The RN study coordinator plays a crucial role in filling the pieces of the puzzle together for a successful result by providing leadership in the research environment.

Why would you want to be a RN study coordinator? For some, the ability to spend more time with patients and their families provides satisfaction. Many nurses working in clinical trials comment on the autonomy afforded them, which capitalizes on nursing professionalism. Many also enjoy the collaborative relationships with other members of the research team and find that such collaboration fits well with nursing. The diversity of work and flexibility of involvement in acute and preventive studies are another attraction for study coordinators. There are opportunities for tremendous professional and personal growth and gratification in this profession. — Louise Durst, RN, PAH Study Coordinator, Mayo Clinic, Rochester, MN

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Table—Practical Tips

<table>
<thead>
<tr>
<th>Manage your files</th>
<th>Keep your electronic and paper files organized and tabbed. If you need help, contact the study sponsor or an experienced study coordinator.</th>
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<tbody>
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<td>Manage your time</td>
<td>Keep a daily to-do list. Keep a calendar with subject appointments and contact information. Complete the case report form; call the subject if clarification is needed.</td>
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<tr>
<td>IRB</td>
<td>Submit on time; do not let a protocol expire. Work on new submissions and collect the pieces in a timely manner, realizing you won’t get everything you need in 1 day.</td>
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<tr>
<td>Contact with the PI</td>
<td>Set up a daily/weekly maintenance meeting. Be organized; have questions written down and items tagged for signature.</td>
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<td>Know your subject</td>
<td>What is their preferred phone number? When is the best time to contact them? Where may you leave a message? Respond to subjects’ questions/concerns immediately.</td>
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<tr>
<td>Sponsor</td>
<td>Respond to requests. Supply required/requested information at monitoring visits; have it ready. Order supplies before you need them. Treat your monitor as a guest.</td>
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A Collaborative Approach for Clinicians on the Front Line

“Excellent didactic presentation and the case presentation also very good...This was one of the better talks on PAH I have attended. There was a good balance of information—all relevant information about all therapies discussed...Excellent speaker, very knowledgeable.” Comments from recent participants

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All programs are scheduled from 7:00-9:30 PM. A complimentary dinner will be provided.

Albany, New York
Speaker: Erika B. Rosenzweig, MD
Tuesday, November 10, 2009

Albuquerque, New Mexico
Speaker: David Badescu, MD
Thursday, December 3, 2009

Augusta, Georgia
Speaker: James Gossage, MD
Tuesday, November 17, 2009

Burlington, Vermont
Speaker: William E. Hopkins, MD
Thursday, October 8, 2009

Champaign/Urbana, Illinois
Speaker: Murali Chakinala, MD
Wednesday, October 28, 2009

Columbia, Missouri
Speaker: Murali Chakinala, MD
Wednesday, November 18, 2009

Helena, Montana
Speaker: Lynn M. Brown, MD, PhD
Tuesday, October 13, 2009

Honolulu, Hawaii
Speaker: Jess Mandel, MD
Tuesday, October 6, 2009

Ithaca, New York
Speaker: Jim White, MD
Wednesday, September 16, 2009

Little Rock, Arkansas
Speaker: Ivan M. Robbins, MD
Wednesday, September 30, 2009

Morgantown, West Virginia
Speaker: Srinivas Murali, MD
Thursday, September 24, 2009

New Orleans, Louisiana
Speaker: Ben deBoisblanc, MD
Wednesday, October 14, 2009

Oklahoma City, Oklahoma
Speaker: Kelly Chin, MD
Thursday, September 17, 2009

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Speaker: Austin Thompson, MD
Wednesday, November 11, 2009

reno, nevada
Speaker: Dana P. McGlothlin, MD
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Spokane, Washington
Speaker: David Ralph, MD
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Speaker: Vallerie V. McLaughlin, MD
Thursday, December 3, 2009

Wichita, Kansas
Speaker: Sonja D. Bartolome, MD
Thursday, December 3, 2009

Worcester, Massachusetts
Speaker: Kimberly Fisher, MD
Wednesday, November 4, 2009

There is no fee for this program.
The progress made in the medical treatment of pulmonary arterial hypertension (PAH) in the past 15 years is unique, in particular for a rare and severe condition: 27 randomized controlled trials (RCTs) have been completed and more than 10 are either ongoing or planned; 8 drugs belonging to 3 pharmacological classes (endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, and prostanoids) and administered by 4 different routes (oral, inhaled, subcutaneous, and intravenous) have been currently approved by the Food and Drug Administration and by the European Medicines Agency. A meta-analysis including 23 published RCTs has shown a 43% reduction in mortality of PAH patients treated with the approved compounds as compared to patients randomized to placebo after 14 weeks of average treatment period. In addition, reductions in the hospitalization rate and improvements of functional and exercise capacity, hemodynamics, and quality of life were also observed. Despite these results, the current treatment strategy remains inadequate because the mortality rate continues to be high and the functional and hemodynamic impairments are still extensive in many patients. The specific drugs approved for PAH are able to slow the progression of the disease, but cannot be considered a cure for the majority of the patients.

The current and future plans devoted to increase our ability to treat PAH are facing new challenges which require scientific creativity and new research strategies.

Paradoxically, there is no shortage of novel candidate therapies for PAH including drugs, gene, and stem cell approaches or combinations of therapies. New drugs with ongoing or planned Phase III studies include oral compounds such as NO-independent stimulators and activators of cGMP, tyrosine kinase inhibitors (platelet-derived growth factor inhibitors), tissue-specific dual endothelin receptor antagonists, prostanoids and non-prostanoid prostacyclin receptor agonists, and inhaled vasoactive intestinal peptide.

The real current difficulty is to identify the most efficient development plan and the more appropriate study designs to demonstrate the efficacy-to-safety ratio of novel therapies in PAH patients. The replication of the traditional Phase III strategy (placebo-controlled design in treatment-naïve patients, exercise capacity as primary end point assessed after 3 to 4 months of treatment) appears not suitable in a changing clinical environment.

It appears not any more ethical to include treatment-naïve patients in placebo-controlled studies in countries with available therapies for PAH. The efficacy-to-safety ratio of the new compounds needs to be demonstrated on top of the available approved drugs for PAH to avoid any delay in the initiation of effective medications. Therefore, future studies with new drugs will be exclusively “combination studies” and “placebo patients” will continue to be treated with traditional compounds. This obviously will reduce our ability to demonstrate a difference with the “actively treated group,” in particular if exercise capacity is the primary end point. This phenomenon has been observed in the more recent completed RCTs in which the treatment effect on the six-minute walk test has been ranging from 15 to 25 meters as compared to the traditional 35 to 55 meters observed in the historical monotherapy studies. A possible solution is the adoption of different primary endpoints acceptable by regulatory agencies such as the combination of morbidity and mortality. Also, this approach presents challenges including the objective definition of the composite endpoint (death, hospitalization, disease progression), the study sample size (event-based vs pre-specified duration), and the lack of precise knowledge of the rate of events with the available treatments. Additional problems of multicenter and international studies are linked to the country-related heterogeneity of PAH-approved medication, of attitudes for hospitalization, and of availability of expert centers.

This extensive list of challenges cannot be considered an excuse to avoid our involvement in current and future RCTs. The traditional enthusiasm and collaboration of the PAH community is currently required to continue the difficult path toward additional advances in this complex field.
GIVE YOUR PAH PATIENTS A SECOND WIND®

NEW Ventavis®

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Please see important safety information on next page and brief summary of full prescribing information on final page.
VENTAVIS is the only inhaled PAH therapy to demonstrate a spectrum of PAH efficacy:

- **Significant** clinical improvement ($p=0.0033$)\textsuperscript{1,2}
- **Significant** functional class improvement ($p=0.03$)\textsuperscript{1,2}
- **Significant** hemodynamic improvement ($p<0.001$)\textsuperscript{1,2}
  (PVR, CO, and mPAP)
- **Significant** 6MWD improvement ($p<0.01$)\textsuperscript{1,2}

**IMPORTANT SAFETY INFORMATION:** In clinical studies, common adverse reactions due to Ventavis included vasodilation (flushing), cough, headache, trismus, and insomnia. Serious adverse events reported at a rate of less than 3% included congestive heart failure, chest pain, supraventricular tachycardia, dyspnea, peripheral edema, and kidney failure. Vital signs should be monitored while initiating Ventavis. Ventavis should not be initiated in patients with systolic blood pressure less than 85 mmHg. Stop Ventavis immediately if signs of pulmonary edema occur; this may be a sign of pulmonary venous hypertension.

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VENTAVIS (iloprost)
20 mcg/mL

A new option to
give appropriate
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treatment times*

• Higher concentration
  —50% reduction in inhaled volume

• Shorter treatment times†

• Helps maintain patient compliance

• Treatment convenience

AIR PIVOTAL TRIAL

Randomized, double-blind, multicenter, placebo-controlled trial to evaluate the efficacy and safety of Ventavis monotherapy in the treatment of PAH NYHA Class III or IV (n=146). Clinical improvement defined as ≥10% increase in 6MWD, improvement in NYHA functional class, and lack of clinical deterioration or death.1,2

*The 20 mcg/mL concentration is intended for patients who are maintained at the 5 mcg dose and who have repeatedly experienced extended treatment times which could result in incomplete dosing. Ventavis 10 mcg/mL ampules are still available. Ventavis should be taken 6 to 9 times daily.2
†Data based on an in vitro study with a manually generated 28.3-L/min, 15-sec inhalation cycle breathing pattern.
BRIEF SUMMARY
The following is a brief summary of the Full Prescribing Information for Ventavis Solution. Please review the Full Prescribing Information prior to prescribing Ventavis.

INDICATIONS AND USAGE
Ventavis is indicated for the treatment of pulmonary arterial hypertension (WHO Group II) in patients with NYHA Class III or IV symptoms. In clinical trials, it improved a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration in COLD-PC (PHARMACOLOGY, Clinical trials section of Full Prescribing Information).

CONTRAINDICATIONS
There are no known contraindications.

WARNINGS
Ventavis is intended for inhalation administration only via either of two pulmonary drug delivery devices: the I-neb® AAD System or the Prodose® AAD® System (see DOSAGE AND ADMINISTRATION section of Full Prescribing Information). It has not been studied with any other nebulizers.

VITAL SIGNS
Vital signs should be monitored while initiating Ventavis. In patients with low hemoglobin, care should be taken to avoid further hypotension. Ventavis should not be initiated in patients with systolic blood pressure less than 85 mmHg. Physicians should be alerted to the presence of concomitant conditions or drugs that might increase the risk of syncope. Syncope can also occur in association with pulmonary arterial hypertensive, particularly in association with exercise. The occurrence of syncope may reflect a therapeutic gap or insufficient efficacy, and the need to adjust dose or change therapy should be considered.

There are no known contraindications.

PRECAUTIONS
General
Ventavis solution should not be allowed to come into contact with the skin or eyes. Oral ingestion of Ventavis solution should be avoided. Direct mixing of Ventavis with other medications in the I-neb® AAD® System or the Prodose® AAD® System has not been evaluated.

Ventavis inhalation can induce bronchospasm, especially in susceptible patients with hyperreactive airways. Ventavis has not been evaluated in patients with chronic obstructive pulmonary disease (COPD), severe asthma, or with acute pulmonary infections. Such patients should be carefully monitored during therapy with Ventavis.

Information for Patients
Patients receiving Ventavis should be advised to use the drug only as prescribed with either of two pulmonary drug delivery devices: the I-neb® AAD® System or the Prodose® AAD® System, following the manufacturer’s instructions (see DOSAGE AND ADMINISTRATION section of Full Prescribing Information). Patients should be trained in proper administration techniques including dosing, de-mistering, I-neb® AAD® System or the Prodose® AAD® System operation, and equipment cleaning. Patients should be advised that they may have a fall in blood pressure with Ventavis, so they may become dizzy or even faint. They should stand up slowly when they get out of a chair or bed. If fainting gets worse, patients should consult their physicians about dose adjustment.

Patients should be advised that Ventavis should be inhaled at intervals of not less than 2 hours and that the acute benefits of Ventavis may last not 2 hours. Thus, patients may want to adjust times of administration to cover planned activities.

Drug Interactions
In studies in normal volunteers, there was no pharmacodynamic interaction seen in patients who were given iloprost and antihypertensive agents. Since iloprost inhibits platelet function, there is a potential for increased risk of bleeding, particularly in patients maintained on anticoagulants. When in clinical trials, iloprost was used concurrently with antiocoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antineoplastics, nonsteroidal anti-inflammatory drugs, corticosteroids, and other medications. Iloprost infusion of iloprost had no effect on the pharmacokinetics of digoxin. Acetylsalicylic acid did not alter the clearance (pharmacokinetics) of iloprost. Although clinically significant studies have not been conducted, in vivo studies of iloprost indicated that no relevant inhibition of cytochrome P450 drug metabolism would be expected.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Iloprost was not mutagenic in bacterial and mammalian cells in the presence or absence of extrinsic mutagenic activation. Iloprost did not cause chromosomal aberrations in human lymphocytes and was not clastogenic in vivo in NMRFF mice. There was no evidence of a tumorigenic effect of iloprost clathrate (13% iloprost by weight) in Sprague-Dawley rats dosed orally for up to 8 months at doses of up to 125 mcg/kg/day (Cmax of 45 ng/mL). Following by 16 months at 100 mcg/kg/day, or in C57-129 (H2O) strain mice dosed orally for up to 24 weeks at doses of up to 125 mcg/kg/day (Cmax of 156 ng/mL). The recommended clinical dosing regimen for iloprost (5 mcg) affords a serum Cmax of 0.16 ng/mL. Fertility of males or females was not impaired in Han-Wistar rats at intravenous doses at up to 1 mg/kg/day.

ADVERSE REACTIONS

ADVERSE REACTIONS
Pre-marketing experiences
Post-marketing safety data on Ventavis were obtained from 215 patients with pulmonary arterial hypertension receiving iloprost in 2 studies performed as part of the I-neb® AAD® System or Prodose® AAD® System post-marketing experience. Over 500 patients participated in Ventavis post-marketing experience.


"Second Wind" is a licensed trademark of Pulmonary Rehabilitation Associates. I-neb AAD is a registered trademark of Philips Respironics.

Table 1: Adverse Events in Phase 3 Clinical Trial

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Iloprost n=101</th>
<th>Placebo n=102</th>
<th>Placebo subtracted %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilation (flushing)</td>
<td>27</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Cough increased</td>
<td>39</td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td>Headache</td>
<td>30</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Trismus</td>
<td>12</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Insomnia</td>
<td>8</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Alt. glos increased</td>
<td>6</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>14</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Back pain</td>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal lab test</td>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Tongue pain</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Palpitations</td>
<td>7</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Syncope</td>
<td>8</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>GIST increased</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Adverse events with higher doses
In a study in healthy volunteers (n=180), inhaled doses of iloprost solution were given every 2 hours, beginning with 5 mcg and increasing up to 20 mcg for a total of 6 dose inhalations (total cumulative dose of 70 mcg) or up to the highest dose tolerated in a subgroup of 40 volunteers. There were 13 subjects (32%) who failed to reach the highest scheduled dose (20 mcg). Five were unable to increase the dose because of (moderate to) transient chest pain/discomfort/ tightness, usually accompanied by headache, nausea, and dizziness. The remaining 8 subjects discontinued for other reasons.

POSTMARKETING EXPERIENCE
The following adverse reactions have been identified during the postapproval use of Ventavis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cases of bronchospasm and wheezing have been reported, particularly in susceptible patients with hyperreactive airways, such as patients with comorbid diseases affecting the airways (see PRECAUTIONS). Cases of epistaxis and gingival bleeding have been reported within one month of starting iloprost treatment. Cases of dizziness and diarrhea have also been reported with the use of Ventavis.

OVERDOSE
In clinical trials of Ventavis, no case of overdose was reported. Signs and symptoms to be anticipated are extensions of the dose-limiting pharmacological effects, including hypotension, headache, flushing, nausea, vomiting, and diarrhea. A specific antidote is not known. Interruption of the inhalation session, monitoring, and symptomatic measures are recommended.

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August 2009
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alert to the presence of concomitant conditions or drugs that might
PRECAUTIONS

Prescribing Information).

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Drug Interactions

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LabSync can:

► Help patients choose a laboratory facility
► Schedule and remind patients of upcoming laboratory appointments
► Assist in resolving insurance-related issues with laboratory testing
► Ensure prescribers receive laboratory test results
► Help determine eligibility for in-home blood draw services when appropriate

LabSync provides centralized support for all required laboratory testing
through a secure website that allows clinicians instant access to patients’
test results and upcoming testing appointments.

To learn more about LabSync, visit www.labsynctalk.com and
register for an interactive teleconference hosted by leading
pulmonary arterial hypertension (PAH) nurses, or speak with
your local Gilead sales specialist.
**Program Description**

This one-day, highly interactive program will offer direct instruction on state-of-the-art PAH diagnosis, initial treatment, and comprehensive long-term management of patients with PAH.

**Educational Objectives**

The *PHA Preceptorship Program* is designed to instruct front-line clinicians in the highest quality of care for patients with PAH. At the conclusion of this program, participants should be able to:

- Define key pathophysiologic and epidemiologic components of PAH
- Accurately diagnose patients through comprehensive screening and early recognition of symptoms
- Evaluate the patient’s condition and prescribe optimal long-term management, including knowing when and how to treat and when to consult with colleagues at an established PAH center
- Tailor comprehensive care for complex patient populations

**Target Audience**

This activity has been designed for pulmonologists, cardiologists, rheumatologists, internists, and primary care physicians, as well as nurses, physician assistants, and other allied health professionals who help care for patients with PAH.

“Our goal is to build links among community PAH specialists, non-specialists, and clinicians at established PAH centers that result in more meaningful collaboration. These new avenues for communication...can help us reach our ultimate goal...better care of our patients with PAH.”

*Todd M. Bull, MD, FACP, Program Chairman*

There is no fee for this program.

The University of Michigan Medical School will provide AMA Category 1 credit for this activity. This activity is jointly sponsored by the University of Michigan Medical School and PHA.

Supported by unrestricted educational grants from:

- **Platinum Sponsor**
- **Gold Sponsors**
- **Silver Sponsor**

For more program information and to register, please visit the PHA website:

[www.PHAssociation.org/Preceptorship](http://www.PHAssociation.org/Preceptorship)
A Program of the Pulmonary Hypertension Association Medical Education Fund

The PHA Preceptorship Program

PAH 09

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ANN ARBOR, MI | BOSTON, MA | DALLAS, TX | DENVER, CO | SAN DIEGO, CA | SAN FRANCISCO, CA

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October 23, 2009 November 13, 2009 November 6, 2009 Date to be announced January 22, 2010

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Emergent adverse events reported by

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be readily extrapolated to the incidence of adverse reactions in routine medical practice.

Clinical Trials Experience

ADCIRCA should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, sickle cell trait, or multiple myeloma), as well as prolonged or repeated exposure to vasodilators. Patients with severely impaired autonomic control of blood pressure or with left ventricular outflow obstruction, as well as those who are receiving alpha-blockers or potent vasodilators, may be at increased risk of fainting.

Drug Interactions

Potential for Pharmacodynamic Interactions with ADCIRCA


tadalafil plasma concentrations.

Before initiating therapy with ADCIRCA, it is recommended to consult the latest data available from clinical trials and a patient's history of prior adverse events.

Use in Renal Impairment

In patients with mild renal impairment, observed tadalafil exposure is 3- to 4-fold greater than that observed in healthy volunteers.

Use in Hepatic Impairment

In patients with moderate hepatic impairment (Child-Pugh Class B), a starting dose of 20 mg once daily is recommended.

Use in Severe Hepatic Impairment

In patients with severe hepatic impairment (Child-Pugh Class C), a starting dose of 20 mg once daily is recommended.

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Building Medical Education in PH

A Partnership Initiative to Advance Medical Understanding of Pulmonary Hypertension

What did these physicians hope to achieve by hosting a pulmonary hypertension continuing education event?

“Our goals were to foster an increased awareness among medical providers, share patient-based experiences in handling the burden of this illness and offer insights into future treatments. From the feedback we received, I believe we achieved these objectives and the help of the PHA was very much appreciated.”

Edward Catherwood, M.D.
3rd Annual Northern New England PH Symposium
Dartmouth-Hitchcock Medical Center

“Our PH Symposium is aimed primarily at educating and updating providers. We try to be as inclusive as possible by inviting providers from all over New England to serve on the faculty, and inviting nurses, other health care professionals and patients in addition to physicians. We had an excellent turnout in 2008 and very enthusiastic feedback. PHA has been a very important component for the patient attendees.”

Nicholas Hill, M.D.
6th Annual Update in Pulmonary Hypertension
Tufts Medical Center

Building Medical Education in PH events are designed to foster partnerships between PHA and PH Centers to promote continuing education in the field of pulmonary hypertension through CME educational events.

To partner with PHA in Building Medical Education in PH for your upcoming CME event, please contact Emily Koenig, Medical Education Program Associate, at 301-565-3004 X776 or Emily@PHAssociation.org.
Program Announcement:

New Application Deadline: February 12, 2010  
Resubmission Deadline: March 12, 2010

New Application Deadline: June 12, 2010  
Resubmission Deadline: July 12, 2010

Pulmonary Hypertension Association (PHA)  
National Heart, Lung, and Blood Institute (NHLBI)

Jointly Sponsored

Mentored Clinical Scientist Development Award (K08) &  
Mentored Patient-Oriented Research Career Development Award (K23)

PURPOSE: K08

• To support the development of outstanding clinician research scientists in the area of pulmonary hypertension.
• To provide specialized study for clinically trained professionals who are committed to a career in research in pulmonary hypertension and have the potential to develop into independent investigators.
• To support a 3 to 5 year period of supervised research experience that integrates didactic studies with laboratory or clinically based research.
• To support research that has both intrinsic research importance and merit as a vehicle for learning the methodology, theories, and conceptualizations necessary for a well-trained independent researcher.

MECHANISM:
Awards in response to the program announcement will use the National Institutes of Health (NIH) K08 or the K23 mechanism.

FUNDING:*  
The award will be funded by PHA and NHLBI and the K08 and/or the K23 will be awarded in 2010.

PURPOSE: K23

• To support career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research.
• To support a 3 to 5 year period of supervised study and research for clinically trained professionals who have the potential to develop into productive, clinical investigators focusing on patient-oriented research in pulmonary hypertension.
• To support patient-oriented research, which is defined as research conducted with human subjects (or on material of human origin, such as tissues, specimens, and cognitive phenomena) for which an investigator directly interacts with human subjects.
• To support areas of research that include: 1) mechanisms of human disease; 2) therapeutic interventions; 3) clinical trials; and 4) development of new technologies.

FOR MORE INFORMATION:  
Visit: www.PHAssociation.org/support/ResearchFunding.asp

* Restrictions apply. Please see complete announcement at the website listed above.