Advances in Pulmonary Hypertension

Prognostication and Risk Prediction for Pulmonary Hypertension

PH Grand Rounds: Rare Coexistence of Major Lung Pathologies
Shimool A. Rabbani, MS IV; Abhijit Raval, MD; Satish Surabhi, MD

Research Reviews
Jonathan D. Rich, MD; Oksana A. Shlobin, MD

Circulating Biomarkers in Pulmonary Arterial Hypertension
Nadine Al-Naamani, MD; Aaron W. Trammell, MD; Zeenat Safdar, MD

Consensus or Controversy: Do Recent Advances Shift the Debate for the Use of Echocardiography Versus Cardiac Magnetic Resonance Imaging of the Right Ventricle in Pulmonary Arterial Hypertension?
Amresh Raina, MD; Benjamin Freed, MD

Prognostication in Pulmonary Arterial Hypertension and Use of Current Risk Prediction Models
Richa Agarwal, MD

Ask the Expert: What Is the Utility of Evaluating Patients for Exercise-Induced Pulmonary Hypertension?
Steven Hsu, MD

Roundtable: Prognostic Indicators for Pulmonary Hypertension
Charles Burger, MD; Ioana R. Preston, MD; Raymond L. Benza, MD; and Jonathan Rich, MD

PH Professional Network: Holistic Assessment of the New Patient With Pulmonary Hypertension: The Role of the Non-Physician Clinician
Melisa Wilson, ARNP, ACNP-BC
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The Scientific Leadership Council of the Pulmonary Hypertension Association

The Scientific Leadership Council is the premier forum for the diagnosis, pathophysiology, and treatment of pulmonary hypertension. The mission of the Scientific Leadership Council is to serve as the premier forum for state of the art information regarding pulmonary hypertension. The mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

The Scientific Leadership Council is comprised of international experts in pulmonary hypertension, with expertise in the diagnosis, pathophysiology, and treatment of PAH, the other categories (Group 2, pulmonary venous hypertension; Group 3, associated with chronic lung disease and/or hypoxemia; Group 4, pulmonary embolic hypertension; Group 5, 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.

Objective
• Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension.

The Scientific Leadership Council is comprised of international experts in pulmonary hypertension, with expertise in the diagnosis, pathophysiology, and treatment of PAH, the other categories (Group 2, pulmonary venous hypertension; Group 3, associated with chronic lung disease and/or hypoxemia; Group 4, pulmonary embolic hypertension; Group 5, 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.

Program Description
The mission of 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 mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

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EDITOR’S MEMO

Editorial Prognostication

It is my honor and pleasure to serve as Editor-in-Chief for Advances in Pulmonary Hypertension volumes 14 and 15. Importantly, I would like to thank Myung Park, MD, for her excellent leadership as past Editor and her support in my transition. The editorial board strives to continually improve the journal under the direction of the Scientific Leadership Council for PHA. Under Dr Park’s leadership, the journal has transformed to meet scientific publication standards and yet remains committed to address important clinical challenges and active areas of inquiry in the scientific understanding of pulmonary hypertension.

In this issue, Drs. Ioana Preston and Ray Benza serve as guest editors and have secured manuscript submissions addressing prognostic risk scoring and cardiac imaging in pulmonary arterial hypertension (PAH). Prognosis, derived from Greek, literally means foreknowledge and may be defined in a medical dictionary as a forecast of probable outcome. As with weather forecasts and the limitation of applying statistical probabilities to individual patients, we are challenged in the determination of prognosis in PAH. Nonetheless, significant progress has been made in this area warranting a whole issue on this important topic.

I would also like to welcome Drs. Jonathan Rich and Oksana Shlobin who have agreed to co-edit a special section entitled Research Review. I would also like to thank Drs. Sean Studer and Deborah Levine for their continued support as section editors. Lastly, Ms. Deborah McBride, managing editor, works tirelessly to bring everything together in a seamless fashion.

I suspect the readers will find this issue both enlightening and provocative and most importantly, clinically applicable.

Charles Burger, MD
Professor of Medicine
Mayo Clinic College of Medicine
Medical Director, PH Clinic
Mayo Clinic, Florida

GUEST EDITORS’ MEMO

Pulmonary hypertension is a rapidly evolving field in which physicians and healthcare professionals are challenged with the complexity of the disease. Assessment of disease severity and determination of risk factors associated with a poor outcome require the integration of multiple parameters derived from clinical practice, clinical trials, and from risk prediction models.

This issue of Advances focuses on these specific tools, which include echocardiography, exercise, and biomarkers, as well as various risk prediction models derived from a number of databases.

From the didactic articles describing prediction parameters to the dynamic discussions at the roundtable and PH Grand Rounds section highlighting their applicability in clinical practice, this issue provides clinicians a description of the multitude and intricacy of tools at their disposition to best assess and treat their patients with pulmonary hypertension. We hope you will appreciate the issue.

Ioana Preston, MD
Co-director, Pulmonary Hypertension Center
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Raymond Benza, MD
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Allegheny Health Network
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Indication

Orenitram is a prostacyclin vasodilator indicated for treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%).

When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this. Orenitram is probably most useful to replace subcutaneous, intravenous, or inhaled treprostinil, but this use has not been studied.

Important Safety Information for Orenitram

CONTRAINDICATIONS

• Orenitram is contraindicated in patients with severe hepatic impairment (Child Pugh Class C)

WARNINGS AND PRECAUTIONS

• Abrupt discontinuation or sudden large reductions in dosage of Orenitram may result in worsening of PAH symptoms
• Orenitram inhibits platelet aggregation and increases the risk of bleeding
• Orenitram should not be taken with alcohol as release of treprostinil from the tablet may occur at a faster rate than intended
• The Orenitram tablet shell does not dissolve. In patients with diverticulosis (blind-end pouches), Orenitram tablets can lodge in a diverticulum

DRUG INTERACTIONS/SPECIFIC POPULATIONS

• Concomitant administration of Orenitram with diuretics, antihypertensive agents, or other vasodilators increases the risk of symptomatic hypotension
• Orenitram inhibits platelet aggregation; there is an increased risk of bleeding, particularly among patients receiving anticoagulants
• Co-administration of Orenitram and the CYP2C8 enzyme inhibitor gemfibrozil increases exposure to treprostinil; therefore, Orenitram dosage reduction may be necessary in these patients
• Pregnancy Category C. Animal reproductive studies with Orenitram have shown an adverse effect on the fetus. There are no adequate and well-controlled studies in humans
• Safety and effectiveness in patients under 18 years of age have not been established
• There is a marked increase in the systemic exposure to treprostinil in hepatically impaired patients

ADVERSE REACTIONS

• In the 12-week placebo-controlled monotherapy study, adverse reactions with rates at least 5% higher on Orenitram than on placebo included headache, diarrhea, nausea, flushing, pain in jaw, pain in extremity, hypokalemia, and abdominal discomfort

Please see brief summary of Full Prescribing Information on following page. For additional information about Orenitram, visit www.orenitram.com or call 1-877-UNITHER (1-877-864-8437).

INDICATIONS AND USAGE
Orenitram is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (73%) or PAH associated with connective tissue disease (19%). When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the direct, and the effect, if any, on a background of another vasodilator is probably less than this. Orenitram is probably most useful to replace subcutaneous, intravenous, or inhaled treprostinil, but this use has not been studied.

CONTRAINDICATIONS
Severe hepatic impairment (Child Pugh Class C).

WARNINGS AND PRECAUTIONS
worsening vasospasm symptoms upon abrupt withdrawal Abrupt discontinuation or sudden large reductions in dosage of Orenitram may result in worsening of PAH symptoms.

Risk of Bleeding—Orenitram inhibits platelet aggregation and increases the risk of bleeding.

Increased exposure to Alcohol—Do not take Orenitram with alcohol as release of treprostinil from the tablet may occur at a faster rate than intended.

Use in Patients with Blind-end Pouches—The tablet shell does not dissolve. In patients with diverticulosis, Orenitram tablets can lodge in a diverticulum.

ADVERSE REACTIONS
Clinical Trial Experience—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 other drug and may not reflect the rates observed in clinical practice. In a 12-week placebo-controlled monotherapy study (Study 1; WHO Group 1; functional class II-III), the most commonly reported adverse reactions that occurred in patients receiving Orenitram included headache, nausea, and diarrhea.

Table 1 lists the adverse reactions that occurred at a rate on Orenitram at least 5% higher than on placebo. Orenitram patients in Table 1 for Study 1 (N = 151) had access to 0.25 mg tablets at randomization. Approximately 91% of such patients experienced an adverse reaction, but only 4% discontinued therapy for an adverse reaction (compared to 3% receiving placebo). The overall discontinuation rate for any reason was 17% for active and 14% for placebo.

Orenitram was studied in a long-term, open-label extension study in which 824 patients were dosed for a mean duration of approximately 2 years. About 70% of patients continued treatment with Orenitram for at least 1 year. The mean dose was 4.2 mg BID at one year. The adverse reactions were similar to those observed in the placebo-controlled trials.

Table 1. Adverse Reactions with Rates at Least 5% Higher on Orenitram Monotherapy than on Placebo

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Orenitram (N=151)</th>
<th>Placebo (N=77)</th>
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<tbody>
<tr>
<td>Headache</td>
<td>63%</td>
<td>19%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>39%</td>
<td>16%</td>
</tr>
<tr>
<td>Nausea</td>
<td>30%</td>
<td>18%</td>
</tr>
<tr>
<td>Flushing</td>
<td>15%</td>
<td>6%</td>
</tr>
<tr>
<td>Pain in jaw</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>6%</td>
<td>0%</td>
</tr>
</tbody>
</table>

No treprostinil treatment related effects on labor and delivery were seen in animal studies.

Nursing Mothers—It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, choose Orenitram or breastfeeding.

Pediatric Use—Safety and effectiveness in pediatric patients have not been established.

Genetic Use—Clinical studies of Orenitram did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic or cardiac function, and of concomitant disease or other drug therapy.

Patients with Hepatic Impairment—Plasma clearance of treprostinil is reduced in patients with hepatic insufficiency. Patients with hepatic insufficiency may therefore be at increased risk of dose-dependent adverse reactions because of an increase in systemic exposure. Titrate slowly in patients with hepatic insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic function. In patients with mild hepatic impairment (Child Pugh Class A) start at 0.125 mg BID with 0.125 mg BID dose increments every 3 to 4 days. Avoid use of Orenitram in patients with moderate hepatic impairment (Child Pugh Class B). Orenitram is contraindicated in patients with severe hepatic impairment (Child Pugh Class C).

Patients with Renal Impairment—No dose adjustments are required in patients with renal impairment. Orenitram is not removed by dialysis.

OVERDOSAGE
Signs and symptoms of overdose with Orenitram during clinical trials reflect its dose-limiting pharmacologic effects and include severe headache, nausea, vomiting, diarrhea, and hypotension. Treat supportively.

Table 1. Adverse Reactions with Rates at Least 5% Higher on Orenitram Monotherapy than on Placebo

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Help your pulmonary hypertension patients gain the knowledge, confidence and hope vital to coping and managing their disease.

Let them know about their local PHA support group.

The Pulmonary Hypertension Association provides “medicine for the soul” in the form of patient support groups. PHA wants to work with you to put patients in touch with each other.

Find Your Local Group
www.PHAssociation.org/FindASupportGroup

No Group? Web and phone support can help. Connect online: www.PHAssociation.org/Community

Toll-free Patient-to-Patient Support: 800-748-7274

Starting a support group has never been easier: From a how-to manual to phone support, PHA works with doctors, nurses and other medical professionals to help start successful groups.

For more information on support groups or to request PHA materials for your office, contact Debbie Drell at DebbieD@PHAssociation.org or 301-565-3004 x755.
Adempas (riociguat) tablets are indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.

Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.* Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominantly patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).

Warnings and Precautions
Adempas REMS Program. Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program.

Important requirements of the Adempas REMS program include the following:

• Prescribers must be certified with the program by enrolling and completing training.

• All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.

Adempas is contraindicated in:

• Pregnancy. Adempas may cause fetal harm when administered to a pregnant woman. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

• Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form.

• Concomitant administration with specific phosphodiesterase-5 (PDE-5) inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline).

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY
Do not administer Adempas (riociguat) tablets to a pregnant female because it may cause fetal harm.

Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.

For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program.
WARNINGS AND PRECAUTIONS (continued)

- Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4ADEMPAS.

Hypotension. Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors. Consider a dose reduction if patient develops signs or symptoms of hypotension.

Bleeding. In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematemesis, and intra-abdominal hemorrhage.

Pulmonary Veno-Oclusive Disease. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and if confirmed, discontinue treatment with Adempas.

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MOST COMMON ADVERSE REACTIONS

- The most common adverse reactions occurring more frequently (≥3%) on Adempas than placebo were headache (27% vs 18%), dyspepsia/gastritis (21% vs. 8%), dizziness (20% vs 13%), nausea (14% vs 11%), diarrhea (12% vs 8%), hypotension (10% vs 4%), vomiting (10% vs 7%), anemia (7% vs 2%), gastroesophageal reflux disease (5% vs 2%), and constipation (5% vs 1%).
- Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema.

For important risk and use information, please see the Brief Summary of the full Prescribing Information, including Boxed Warning, on the next page.

See what Adempas could do for your patients.

Visit Adempas-US.com

Stimulating
It means different things to different people.

†Soluble Guanylate Cyclase

FOR PAH. FOR CTEPH.

Adempas® riociguat tablets
0.5mg | 1mg | 1.5mg | 2mg | 2.5mg
ADEMPAS (riociguat) tablets, for oral use
Initial U.S. Approval: 2013

BRIEF SUMMARY of PRESCRIBING INFORMATION
For additional information, please see the full Prescribing Information at www.adempas-us.com.

WARNING: EMBRYO-FETAL TOXICITY
See full prescribing information for complete boxed warning
• Do not administer Adempas to a pregnant female because it may cause fetal harm. (4.1, 5.1, 8.1)
• Females of reproductive potential: Exclude pregnancy before start of treatment, monthly during treatment, and 1 month after treatment discontinuation. Prevent pregnancy during treatment and for one month after treatment discontinuation by use of acceptable methods of contraception. (2.3, 5.1, 5.2, & 5.8).
• For females, Adempas is available only through a restricted program called the Adempas REMS Program. (5.1, 5.2).

1 INDICATIONS AND USAGE
1.1 Chronic-Thromboembolic Pulmonary Hypertension
Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class (see Clinical Studies (14.1)).

1.2 Pulmonary Arterial Hypertension
Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.

Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominantly patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%) (see Clinical Studies (14.2)).

4 CONTRAINDICATIONS
4.1 Pregnancy
Adempas may cause fetal harm when administered to a pregnant woman. Adempas is contraindicated in females who are pregnant. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus (see Use in Specific Populations (8.1)).

4.2 Nitrates and Nitric Oxide Donors
Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated (see Drug Interactions (7.2) and Clinical Pharmacology (12.2)).

4.3 Phosphodiestrase Inhibitors
Concomitant administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) is contraindicated (see Drug Interactions (7.1) and Clinical Pharmacology (12.2)).

5 WARNINGS AND PRECAUTIONS
5.1 Embryo-Fetal Toxicity
Adempas may cause fetal harm when administered during pregnancy and is contraindicated for use in women who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, advise use of acceptable contraception and obtain monthly pregnancy tests. For females, Adempas is only available through a restricted program under the Adempas REMS Program (see Dosage and Administration (2.3), Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.6)).

5.2 Adempas REMS Program
Females can only receive Adempas through the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program, a restricted distribution program (see Warnings and Precautions (5.1)). Important requirements of the Adempas REMS Program include the following:
• Prescribers must be certified with the program by enrolling and completing training.
• All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program.
• Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements (see Use in Specific Populations (8.6)).
• Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.

Further information, including a list of certified pharmacies, is available at www.AdempasREMS.com or 1-855-4 ADEMPAS.

5.3 Hypotension
Adempas reduces blood pressure. Consider the potential for symptomatic hypotension or ischemia in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension, autonomic dysfunction, or concomitant treatment with antihypertensives or strong CYP and P-gp/BCRP inhibitors (see Drug Interactions (7.2) and Clinical Pharmacology (12.2)). Consider a dose reduction if patient develops signs or symptoms of hypotension.

5.4 Bleeding
In the placebo-controlled clinical trials, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0% of placebo patients. Serious hemoptysis occurred in 5 (1%) patients taking Adempas compared to 0 placebo patients, including one event with fatal outcome. Serious hemorrhagic events also included 2 patients with vaginal hemorrhage, 2 with catheter site hemorrhage, and 1 each with subdural hematoma, hematremesis, and intra-abdominal hemorrhage.

5.5 Pulmonary Veno-Occlusive Disease
Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD). Therefore, administration of Adempas to such patients is not recommended. Should signs of pulmonary edema occur, the possibility of associated PVOD should be considered and, if confirmed, discontinue treatment with Adempas.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:
• Embryo-Fetal Toxicity (see Warnings and Precautions (5.1))
• Hypotension (see Warnings and Precautions (5.3))
• Bleeding (see Warnings and Precautions (5.4)).

6.1 Clinical Trials Experience

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.

The safety data described below reflect exposure to Adempas in two, randomized, double blind, placebo-controlled trials in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH patients (PATENT-1). The population (Adempas: n = 490; Placebo: n = 214) was between the age of 18 and 80 years (see Clinical Studies (14.1, 14.2)).

The safety profile of Adempas in patients with inoperable or recurrent/persistent CTEPH (CHEST-1) and treatment naive or pre-treated PAH (PATENT-1) were similar. Therefore, adverse drug reactions (ADRs) identified from the 12 and 16-week placebo-controlled trials for PAH and CTEPH respectively were pooled, and those occurring more frequently on Adempas than placebo (≥3%) are displayed in Table 1 below. Most adverse reactions in Table 1 can be ascribed to the vasodilatory mechanism of action of Adempas.

The overall rates of discontinuation due to an adverse event in the pivotal placebo-controlled trials were 2.9% for Adempas and 5.1% for placebo (pooled data).

Table 1: Adverse Reactions Occurring More Frequently (≥3%) on Adempas than Placebo (Pooled from CHEST-1 and PATENT-1)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Adempas % (n=490)</th>
<th>Placebo % (n=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Dyspepsia and Gastritis</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Nausea</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Anemia (including laboratory parameters)</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema. With longer observation in uncontrolled long-term extension studies the safety profile was similar to that observed in the placebo controlled phase 3 trials.

7 DRUG INTERACTIONS

7.1 Pharmacodynamic Interactions with Adempas

Nitrates: Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form is contraindicated because of hypotension (see Contraindications (4.2) and Clinical Pharmacology (12.2)).

PDE Inhibitors: Co-administration of Adempas with specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) and nonspecific PDE inhibitors (such as dipyridamole or theophylline), is contraindicated because of hypotension (see Contraindications (4.3) and Clinical Pharmacology (12.2)). Clinical experience with co-administration of Adempas and

...
other phosphodiesterase inhibitors (for example, milrinone, cilostazol, roflumilast) is limited.

7.2 Pharmacokinetic Interactions with Adempas

Smoking: Plasma concentrations in smokers are reduced by 50-60% compared to nonsmokers. Based on pharmacokinetic modeling, for patients who are smokers, doses higher than 2.5 mg three times a day may be considered in order to match exposure seen in nonsmoking patients. Safety and effectiveness of Adempas doses higher than 2.5 mg three times a day have not been established. A dose reduction should be considered in patients who start smoking [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].

Strong CYP3A4 and V-gp/BCB4H inhibitors: Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-gp/BCRP inhibitors such as azole antifungals (for example, ketoconazole, itraconazole), P-gp protease inhibitors (such as ritonavir) increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg 3 times a day when initiating Adempas in patients receiving strong CYP and P-gp/BCRP inhibitors. Monitor for signs and symptoms of hypotension on initiation and every 3-7 days for at least 2 months; if required, consider dose adjustments or discontinuation if severe hypotension occurs. A dose reduction should be considered in patients who may not tolerate the hypotensive effect of riociguat [see Dosage and Administration (2.5), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

Strong CYP3A inducers: Strong inducers of CYP3A (for example, rifampin, phenytoin, carbamazepine, phenobarbital or St. John’s Wort) may significantly reduce riociguat exposure. Data are not available to guide dosing of riociguat when strong CYP3A inducers are co-administered [see Clinical Pharmacology (12.3)].

Antacids: Antacids such as aluminum hydroxide/magnesium hydroxide decrease riociguat absorption and should not be taken within 1 hour of taking Adempas [see Clinical Pharmacology (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary
Adempas may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Adempas was teratogenic and embryotoxic in rats at doses with exposures to unbound drug that were approximately 8 times and 2 times, respectively, the human exposure. In rabbits, riociguat led to abortions at 4 times the human exposure and fetal toxicity at exposures approximately 13 times the human exposure. If Adempas is used in pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus [see Boxed Warning and Contraindications (4.1)].

An infant

In rats administered riociguat orally (1, 5, and 25 mg/kg/day) throughout organogenesis, an increased rate of cardiac ventricular-septal defect was observed at the highest dose tested. The highest dose produced evidence of maternal toxicity (reduced body weight). Post-implantation loss was statistically significantly increased from the mid-dose of 5 mg/kg/day. Plasma exposure at the lowest dose in which no adverse effects were observed is approximately 0.4 times that in humans at the maximally recommended human dose (MRHD) of 2.5 mg three times a day based on area under the time-concentration curve (AUC) for unbound drug in rat and human. Plasma exposure at the highest dose (25 mg/kg/day) is approximately 8 times that in humans at the MRHD while exposure at the mid-dose (5 mg/kg/ day) is approximately 2 times that in humans at the MRHD. In rabbits given doses of 0.5, 1.5 and 5 mg/kg/day, an increase in spontaneous abortions was observed at the mid-dose of 1.5 mg/kg, and an increase in resorptions was observed at 5 mg/kg/day. Plasma exposures at these doses were 4 times and 13 times, respectively, the human exposure at the MRHD.

8.3 Nursing Mothers

It is not known if Adempas is present in human milk. Riociguat or its metabolites were present in the milk of rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from riociguat, discontinue nursing or Adempas.

8.4 Pediatric Use

Safety and effectiveness of Adempas in pediatric patients have not been established [see Nonclinical Toxicology (13.2)].

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Adempas, 23% were 65 and over, and 6% were 75 and over [see Clinical Studies (14)]. No overall differences in safety or effectiveness were observed between these two age groups. The dose of Adempas was increased in younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients showed a higher exposure to Adempas [see Clinical Pharmacology (12.3)].

8.6 Females and Males of Reproductive Potential

Pregnancy Testing: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with Adempas, monthly during treatment, and one month after discontinuation of treatment with Adempas. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus [see Boxed Warning, Dosage and Administration (2.3) and Use in Specific Populations (8.1)].

Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with Adempas and for 1 month after treatment with Adempas. Patients may choose one highly effective form of contraception (intrauterine device [IUD], contraceptive implants or tubal sterilization) or a combination of methods (hormone if used with a barrier method or two barrier methods). If a patient’s vasoctomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception and, or designate counseling by another healthcare provider trained in contraceptive counseling [see Boxed Warning].

8.7 Renal Impairment

Safety and efficacy have not been demonstrated in patients with creatinine clearance <15 mL/min or on dialysis [see Clinical Pharmacology (12.3)].

8.8 Hepatic Impairment

Safety and efficacy have not been demonstrated in patients with severe hepatic impairment (Child Pugh C) [see Clinical Pharmacology (12.3)].

10 OVERDOSAGE

In cases of overdose, blood pressure should be closely monitored and supported as appropriate. Based on extensive plasma protein binding, riociguat is not expected to be dialyzed.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Embryo-Fetal Toxicity

Instruct patients on the risk of fetal harm when Adempas is used during pregnancy [see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]. Instruct females of reproductive potential to use effective contraception and to contact the physician immediately if they suspect they may be pregnant. Female patients must enroll in the Adempas REMS Program.

Adempas REMS Program

For female patients, Adempas is available only through a restricted program called the Adempas REMS Program [see Warnings and Precautions (5.2)]. Male patients are not enrolled in the Adempas REMS Program.

Inform female patients (and their guardians, if applicable) of the following important requirements:

• All female patients must sign an enrollment form.
• Advise female patients of reproductive potential that she must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (8.1)].
• Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or contraceptive failure.
• Advise pre-pubertal females to report any changes in their reproductive status immediately to her prescriber.

Review the Medication Guide and REMS educational materials with female patients.

Other Risks Associated with Adempas

• Inform patients of the contraindication of Adempas with nitrates or nitric oxide donors or PDE-5 inhibitors.
• Advise patients about the potential risks/signs of hemoptysis and to report any potential signs of hemoptysis to their physicians.
• Instruct patients on the dosing, titration, and maintenance of Adempas.
• Advise patients regarding activities that may impact the pharmacology of Adempas (strong multi pathway CYP inhibitors and P-gp/BCRP inhibitors and smoking). Patients should report all current medications and new medications to their physician.
• Advise patients that antacids should not be taken within 1 hour of taking in Adempas.
• Inform patients that Adempas can cause dizziness, which can affect the ability to drive and use machines [see Adverse Reactions (6.1)]. They should be aware of how they react to Adempas, before driving or operating machinery and if needed, consult their physician.

Manufactured for: Bayer HealthCare
Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981
Manufactured in Germany

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6710501BS
Important Safety Information

CONTRAINDICATIONS

- **Nitrates**: ADCIRCA should not be used in patients taking medicines that contain nitrates, as the combination could cause a sudden, unsafe drop in blood pressure
- **Hypersensitivity Reactions**: Patients with a known serious hypersensitivity to tadalafl should not take ADCIRCA

WARNINGS AND PRECAUTIONS

- **Cardiovascular**: Patients who experience anginal chest pain after taking ADCIRCA should seek immediate medical attention
- **Cardiovascular**: Phosphodiesterase 5 inhibitors (PDE-5is), including tadalafl, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Before prescribing ADCIRCA, physicians should carefully consider whether their patients with underlying cardiovascular disease could be adversely affected by such actions. Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease (PVOD) and administration of ADCIRCA to these patients is not recommended
- **Cardiovascular**: The use of ADCIRCA with alpha blockers, blood pressure medications, or alcohol may lower blood pressure significantly and may lead to symptomatic hypotension (light-headedness or fainting)
- **Potential Drug Interactions**: Tadalafl is metabolized predominately by CYP3A in the liver. Use of ADCIRCA with potent CYP3A inhibitors, such as ketoconazole and itraconazole, should be avoided. For patients on ADCIRCA therapy that require treatment with ritonavir, ADCIRCA should be discontinued at least 24 hours prior to starting ritonavir. For patients on ritonavir therapy that require treatment with ADCIRCA, start ADCIRCA at 20 mg once a day. Use of ADCIRCA with potent inducers of CYP3A, such as rifampin, should be avoided
- **Special Populations**: The use of ADCIRCA is not recommended for patients with severe renal or hepatic impairment. Please see Full Prescribing Information for dosing recommendations for patients with mild to moderate renal or hepatic impairment
- **Potential Drug Interactions**: ADCIRCA contains the same ingredient (tadalafl) as Cialis®, which is used to treat erectile dysfunction (ED) and the signs and symptoms of benign prostatic hyperplasia (BPH). The safety and efficacy of combinations of ADCIRCA with Cialis or other PDE-5is have not been studied. Therefore, the use of such combinations is not recommended
- **Vision/Hearing**: Patients who experience a sudden loss of vision in one or both eyes, which could be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), or sudden decrease or loss of hearing after taking ADCIRCA should seek immediate medical attention
A diagnosis of pulmonary arterial hypertension (PAH) CAN STOP A PATIENT IN THEIR TRACKS

Take the first step forward to a solid foundation with ADCIRCA® (tadalafil), a first-line therapy for PAH.

ADCIRCA® (tadalafil) is a phosphodiesterase 5 inhibitor (PDE-5i) indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

- Prolonged Erection: In rare instances, men taking PDE-5is (including tadalafil) for ED reported an erection lasting more than four hours. Male patients who experience a prolonged erection should seek immediate medical attention

ADVERSE REACTIONS

- Adverse Reactions: The most common adverse event with ADCIRCA is headache (42% ADCIRCA vs 15% placebo). Other common adverse events (reported by ≥ 9% of patients on ADCIRCA and more frequent than placebo by 2%) include myalgia (14% vs 4%), nasopharyngitis (13% vs 7%), flushing (13% vs 2%), respiratory tract infection (13% vs 6%), extremity pain (11% vs 2%), nausea (11% vs 6%), back pain (10% vs 6%), dyspepsia (10% vs 2%), and nasal congestion (9% vs 1%)

Help your patients move forward with ADCIRCA—one step at a time.

For patients taking ADCIRCA in comparison to patients on placebo at 16 weeks, the average increase from baseline in 6-minute walk distance was 33 meters (108 feet) for all patients* and 44 meters (144 feet) for those on ADCIRCA monotherapy.1,2

Clinically proven to reduce risk of clinical worsening vs placebo at 16 weeks1,2

The recommended dose of ADCIRCA is 40 mg (two 20-mg tablets) taken once-daily, with or without food. Dividing the dose is not recommended

The only once-daily PDE-5 inhibitor for PAH1

The most common (reported by ≥ 13% of patients) treatment-emergent side effects of ADCIRCA (headache, myalgia, nasopharyngitis, flushing, and respiratory infection) were transient and mild to moderate in intensity1

$20 co-pay for eligible patients on commercial/private insurance plans4

*Includes patients on monotherapy and background bosentan therapy.1,2

1Clinical worsening is defined as death, lung transplantation, atrial septostomy, hospitalization because of worsening PAH, initiation of new PAH therapy (prostacyclin or analog, endothelin receptor antagonist, PDE-5 inhibitor), or worsening WHO functional class.1

Patients must meet certain eligibility criteria to qualify for assistance. Patients receiving reimbursement under Medicare, Medicaid, VA, DoD (TRICARE), Indian Health Services, or similar federal or state programs, may not be eligible for some assistance. Some portion of this patient assistance may be administered by Caring Voice Coalition (CVC), an independent national nonprofit organization.

ADCIRCA and Cialis are registered trademarks of Eli Lilly and Company, 2014.


Please see Brief Summary of Full Prescribing Information on following page. Please see Full Prescribing Information and Patient Information available at www.adcirca.com, or call 1-800-545-5979.
**ADCRICA® (tadalafil) tablets**

**BRIEF SUMMARY**

The following is a brief summary of the Full Prescribing Information on ADCIRCA (tadalafil). Please review the Full Prescribing Information prior to prescribing ADCIRCA.

**INDICATIONS AND USAGE**

**Pulmonary Arterial Hypertension:** ADCIRCA is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in adults. Studies establishing effectiveness included predominately patients with NYHA Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (33%).

**CONTRAINdications**

Do not use ADCIRCA in patients who are using any form of organic nitrite, either regularly or intermittently. ADCIRCA potentiates the hypotensive effect of nitrates. This potentiation is thought to result from the combined effect of nitrates and ADCIRCA on the nitric oxide/cGMP pathway. Hypersensitivity Reactions: ADCIRCA is contraindicated in patients with a known severe hypersensitivity to tadalafil (ADCRICA or CIALIS). Hypersensitivity reactions have been reported, including Stevens-Johnson syndrome and exfoliative dermatitis.

**WARNINGS AND PRECAUTIONS**

**Cardiovascular Effects:** Discuss with patients the appropriate action to take in the event that they experience anginal chest pain following intake of ADCIRCA. A least 48 hours should elapse after the last dose of ADCIRCA before taking nitrates. If a patient has taken ADCIRCA within 48 hours, administer nitrates under close medical supervision with appropriate hemodynamic monitoring. Patients who experience anginal chest pain after taking ADCIRCA should seek immediate medical attention. PDE5 inhibitors, including tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing ADCIRCA, carefully consider whether patients with underlying cardiovascular disease could be affected adversely by such vasodilatory effects. Patients with severely impaired autonomic control of blood pressure or with left ventricular outflow obstruction, (e.g., aortic stenosis and idioapatic hyperrophic subaortic stenosis) may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors. Pulmonary vasodilation may occur after arterial and venous stenosis in patients with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of ADCIRCA to patients with veno-occlusive disease, administration of ADCIRCA to such patients is not recommended. Should signs of pulmonary edema occur when ADCIRCA is administered, the possibility of associated PVOD should be considered. There is a lack of data on safety and efficacy in the following groups who were specifically excluded from the PAH clinical trials:

- Patients with clinically significant aortic and mitral valve disease
- Patients with peripheral constriction
- Patients with restrictive or congestive cardiomyopathy
- Patients with significant left ventricular dysfunction
- Patients with life-threatening arrhythmias
- Patients with symptomatic coronary artery disease
- Patients with hypertension (~90/50 mm Hg) or uncontrolled hypertension

Use with Alpha Blockers and Antihypertensives — PDE5 inhibitors, including ADCIRCA, and alpha-adrenergic blocking agents are vasodilators with blood pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may occur. Patients may experience symptoms of hypotension. Use with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomic deformation of the penis (such as angulation, curvature, or Peyronie’s disease).

**Effects on Bleeding:** FDOT is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. ADCIRCA has not been shown to increase bleeding times in healthy subjects, use in patients with bleeding disorders or significant active peptic ulceration should be based upon a careful risk-benefit assessment.

**ADVERSE REACTIONS**

The following serious adverse reactions are discussed elsewhere in the labeling:

- Hypotension
- Visual loss
- Hearing loss
- Priapism

**Clinical Trials Experience:** 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. Tadalafil was administered to 396 patients with PAH during clinical trials worldwide. In trials of ADCIRCA, a total of 311 and 251 subjects have been treated for at least 182 days and 360 days, respectively. The overall rates of discontinuation because of an adverse event (AE) in the placebo-controlled trial were 9% for ADCIRCA 40 mg and 15% for placebo. The rates of discontinuation because of AEs, other than those related to worsening of PAH, in patients treated with ADCIRCA 40 mg was 4% compared to 5% in placebo-treated patients. In the placebo-controlled study, most of the common AEs were generally transient and mild to moderate in intensity. Table 1 presents treatment-emergent adverse events reported by ≥2% of patients in the ADCIRCA 40 mg group and occurring more frequently than with placebo.

**TABLE 1:** Treatment-Emergent Adverse Events Reported by ≥2% of Patients in ADCIRCA and More Frequent than Placebo by 2%

<table>
<thead>
<tr>
<th>EVENT</th>
<th>ADCIRCA 20 mg (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Myalgia</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Back Pain</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

**Postmarketing Experience:** The following adverse reactions have been identified during post-approval use of tadalafil.

These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including ADCIRCA. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. Patients should be informed that if these events occur, they should discontinue their PDE5 inhibitors.

**Combination with Other PDE5 Inhibitors:** Tadalafil is also marketed as CIALIS. The safety and efficacy of taking ADCIRCA together with CIALIS or other PDE5 inhibitors have not been studied. Inform patients taking ADCIRCA not to take CIALIS or other PDE5 inhibitors.

**Erectile Dysfunction:** There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections) lasting greater than 6 hours in duration for this class of compounds. Priapism, if not treated promptly, can result in irreversible damage to the erectile tissue. Patients who have an erection lasting greater than 4 hours, whether painful or not, should seek emergency medical attention. ADCIRCA should be used with caution in patients who have conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukemia), or in patients with anatomic deformation of the penis (such as angulation, curvature, or Peyronie’s disease).

**Hearing Impairment:** Hearing loss requiring discontinuation of a PDE5 inhibitor, including tadalafil, has been reported to occur shortly after the use of tadalafil without sexual activity. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or other factors. Patients should be informed that if these events occur, they should stop their PDE5 inhibitors.
combination of these factors, or to other factors. 

**OTOLITHIC** — Cases of sudden decrease or loss of hearing have been reported postmarketing in temporal association with the use of PDE5 inhibitors, including tadalafil. In some of the cases, medical conditions and other factors were reported that may have also played a role in the otologic adverse events. In many cases, medical follow-up information was limited. It is not possible to determine whether these reported events are related directly to the use of tadalafil, to the patient’s underlying risk factors for hearing loss, a combination of these factors, or to other factors.

**UROGENITAL** — Priapism.

**DRUG INTERACTIONS**

Potential for Pharmacodynamic Interactions with are using any form of organic nitrate. In clinical pharmacology studies ADCIRCA potentiates the hypotensive effect of nitrates. In a patient who has taken ADCIRCA, where nitrate administration is deemed medically necessary in a life-threatening situation, at least 48 hours should elapse after the last dose of ADCIRCA before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring.

**Alpha-Blockers** — PDE5 inhibitors, including ADCIRCA, and alpha-adrenergic blocking agents are both vasodilators with blood-pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. Clinical pharmacology studies have been conducted with coadministration of tadalafil with doxazosin, alfuzosin or tamsulosin.

**Antihypertensives** — PDE5 inhibitors, including ADCIRCA, are mild systemic vasodilators. Clinical pharmacology studies were conducted to assess the effect of tadalafil on the potentiation of the blood-pressure-lowering effects of selected antihypertensive medications (amlodipine, angiotensin II receptor blockers, bendroflumethiazide, enalapril, and metoprolol). Small reductions in blood pressure occurred following coadministration of tadalafil with these agents compared with placebo.

**Alcohol** — Both alcohol and tadalafil, a PDE5 inhibitor, act as mild vasodilators. When mild vasodilators are taken in combination, blood pressure-lowering effects of each individual compound may be increased. Substantial consumption of alcohol (e.g., 5 units or greater) in combination with ADCIRCA can increase the potential for orthostatic signs and symptoms, including increase in heart rate, decrease in standing blood pressure, dizziness, and headache. Tadalafil (10 mg or 20 mg) did not affect alcohol plasma concentrations and alcohol did not affect tadalafil plasma concentrations.

**Potential for Other Drugs to Affect ADCIRCA:**

**Ritonavir** — Ritonavir initially inhibits and later induces CYPS, the enzyme involved in the metabolism of tadalafil. At steady state of ritonavir (about 1 week), the exposure to tadalafil is similar as in the absence of ritonavir.

**Other Potent Inhibitors of CYPS** — Tadalafil is metabolized predominantly by CYPS 3A4 in the liver. In patients taking potent inhibitors of CYPS such as ketoconazole, and itraconazole, avoid use of ADCIRCA.

**Potential Inducers of Cytochrome P450** — For patients chronically taking potent inducers of CYPS, such as rifampin, avoid use of ADCIRCA.

**Potential for ADCIRCA to Affect Other Drugs:**

**Cytchrome P450 Substrates** — Tadalafil is not expected to cause clinically significant inhibition or induction of the clearance of drugs metabolized by cytochrome P450 (CYP) isoforms (e.g., theophylline, warfarin, midazolam, lovastatin, bosentan). Aspirin — Tadalafil (10 mg and 20 mg once daily) does not potentiate the increase in bleeding time caused by aspirin.

**Use in Specific Populations**

**Pregnancy:** Pregnancy Category B — Animal reproduction studies in rats and mice revealed no evidence of fetal hazard. There are, however, no adequate and well-controlled studies of tadalafil in pregnant women. Because animal reproduction studies are not always predictive of human response, tadalafil should be used during pregnancy only if clearly needed.

**Non-teratogenic effects** — Animal reproduction studies showed no evidence of teratogenicity, embryotoxicity, or fetotoxicity when tadalafil was given to pregnant rats or mice at unbound tadalafil exposures up to 7 times the maximum recommended human dose (MRHD) of 40 mg/day during organogenesis. In one of two perinatal/postnatal developmental studies in rats, postnatal pup survival decreased following maternal exposure to unbound tadalafil concentrations greater than 5 times the MRHD based on AUC. Signs of maternal toxicity occurred at doses greater than 8 times the MRHD based on AUC. Surviving offspring had normal development and reproductive performance.

**Nursing Mothers:** It is not known whether tadalafil is excreted into human milk. While tadalafil or some metabolite of tadalafil was excreted into rat milk, drug levels in animal breast milk may not accurately predict levels of drug in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ADCIRCA is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness of ADCIRCA in pediatric patients have not been established.

**Geriatric Use:** Of the total number of subjects in the clinical study of tadalafil for pulmonary arterial hypertension, 28 percent were 65 and over, while 8 percent were 75 and over. No overall differences in safety were observed between subjects over 65 years of age compared to younger subjects or those over 75 years of age. No dose adjustment is warranted based on age alone; however, a greater sensitivity to medications in some older individuals should be considered.

**Renal Impairment:** For patients with mild or moderate renal impairment, start ADCIRCA at 20 mg once daily. Increase the dose to 40 mg once daily based on individual tolerability. In patients with severe renal impairment, avoid use of ADCIRCA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.

**Hepatic Impairment:** Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A or B), consider a starting dose of ADCIRCA 20 mg once daily. Patients with severe hepatic cirrhosis (Child-Pugh Class C) have not been studied, thus avoid use of ADCIRCA in such patients.

**OVERDOSAGE**

Single doses up to 500 mg have been given to healthy male subjects, and multiple daily doses up to 100 mg have been given to male patients with erectile dysfunction. Adverse reactions were similar to those seen at lower doses. Doses greater than 40 mg have not been studied in patients with pulmonary arterial hypertension. In cases of overdose, standard supportive measures should be adopted as needed. Hemodialysis contributes negligibly to tadalafil elimination.

**Marketed by:** Lung Biotechnology Inc., a wholly-owned subsidiary of United Therapeutics Corporation

Rx only


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www.adcirca.com

On Thursday, Sept. 17, PHA’s PH Professional Network Symposium will kick-off with PHPN Advocacy Day on Capitol Hill. This is a rare, critical opportunity for healthcare professionals to represent the needs of PH patients before congress.

PHPN Advocacy Day to Focus on Access to Treatment

This year, Advocacy Day participants will focus on ensuring that PHers have access to the treatment their physician thinks is best for them. Advocates will talk with legislators about the burden created by fail-first policies, high co-insurance and other treatment barriers.

Encourage Your Team to Join PHA for this Free Event, Thursday, Sept. 17

PHPN Advocacy Day is free and open to all. No previous advocacy experience is needed. Signing up is as simple as checking the Advocacy Day box on the PHPN Symposium registration form.

For more information, visit
www.PHAssociation.org/Symposium/AdvocacyDay.
PH GRAND ROUNDS

Rare Coexistence of Major Lung Pathologies

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AnMed Heart Health and Vascular Care
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Presentation: A 40-year-old African American female with past history of congenital heart murmurs of unknown etiology, iron deficiency anemia, and intellectual disability secondary to newborn shaken baby syndrome presented to the emergency department with worsening dyspnea, cough, sore throat, and fatigue. Family history was significant for Wegener’s granulomatosis and lung cancer. Social history was negative for tobacco, alcohol, or illicit drug use. She lives at home with her sister as her legal caregiver. Workup revealed tachycardia, III/VI holosystolic murmur, right axis deviation on electrocardiogram (EKG), and respiratory alkalosis on arterial blood gas (ABG). She was found to have bilateral upper lobe infiltrates and hilar lymphadenopathy as well as an enlarged pulmonary artery on computed tomography (CT) scan (Figure 1). She was admitted and treated empirically for pneumonia with antibiotics without clinical improvement. She was then referred to the pulmonary clinic for further clinical workup and evaluation of radiographic changes.

Assessment: A pulmonary function test at her outpatient workup indicated a mild restrictive pattern with a total lung capacity of 74% and FEV1/FVC at 84%. Bronchoscopy was performed and analysis of the bronchoscopic lavage was negative for all cultures and flow cytometry. Endobronchial ultrasound-guided fine-needle aspiration noted noncaseating granuloma (Figure 2). Gallium scan showed uptake in both hilar regions and bilateral upper lobes (Figure 3). Echocardiogram revealed severe tricuspid regurgitation and an enlarged right ventricular (RV) cavity with hypokinesis of the RV free wall and severely reduced RV systolic function. A follow-up dobutamine stress test was negative for any evidence of ischemia. Her blood work indicated a slightly elevated ACE level at 68, but ESR, CRP, PT/PTT, HIV, RF, and ANA were within normal limits. Right heart catheterization (RHC) noted severe pulmonary arterial hypertension (PAH) (Table 1, Figure 4a).

Therapy and Follow-up: The patient was diagnosed with sarcoidosis-associated pulmonary hypertension (SAPH) and stage II sarcoidosis due to hilar lymphadenopathy and minor parenchymal involvement as noted on the radiographic imaging. Treatment was initiated with prednisone and bosentan. At her 3-month follow-up she was noted to have a favorable response to the therapy, as evidenced by a drop in ACE level, improvement in cough, and an improvement in her 6-minute walk test (6MWT) from 113 m to 153 m. However, 6 months later, her condition deteriorated with worsening dyspnea, and she was subsequently hospitalized for a repeat evaluation. A ventilation-perfusion (V/Q) scan revealed multiple wedge-shaped defects suggestive of pulmonary thromboembolism, which prompted further evaluation with a CT angiogram (CTA) (Figure 5). The CTA noted mediastinal fibrosis with compressive effects, peripheral pruning, and central pulmonary arterial enlargement with no clear emboli. A repeat RHC showed deteriorating PAH (Table 1, Figure 4b). The patient’s sarcoidosis alone could not account for the severity of the PAH; therefore, a pulmonary angiogram was performed. It revealed focal subsegmental stenosis of 70% to 80% in the right upper, right lower, and left lower arterioles (Figure 6). Following the findings on the pulmonary angiogram and CTA, she was diagnosed with PAH secondary to peripheral pulmonary artery stenosis (PPS). The patient was nonresponsive to vasodilator challenge (epoprostenol) and was subsequently started on inhaled treprostinil and sildenafil. This provided mild symptomatic relief while surgical treatments were explored. She was evaluated at multiple transplant centers for lung transplantation, but did not qualify due to intellectual disability. At this point, pulmonary artery stenting to relieve PAH secondary to PPS was considered. Following placement of the pulmonary artery stents, she was noted to have decreased dyspnea on exertion. A pulmonary angiogram revealed significant improvement in her hemodynamics.
and pulmonary arterial flow (Figure 7). She was able to walk 356 m on her 6MWT as compared to 153 m before stenting. She was weaned off the inhaled treprostinil but continued on sildenafil and bosentan. At 1-year follow-up, her sister reported substantial improvement in quality of life with consistent maintenance of her 6MWT, and she was able to go back to her daily living activities, including swimming in the Special Olympics.

**Discussion:** This is a rare case of acquired PPS from sarcoidosis-mediated mediastinal fibrosis, as noted by the compressive effects on the CT scan. However, it is believed that a stage II sarcoidosis with minor parenchymal involvement and hilar lymphadenopathy is not significant enough to cause her suprasystemic right ventricular systolic pressure (RVSP). With her history of congenital heart murmur, it is hypothesized that she most likely had undiagnosed congenital PPS with mild hemodynamic effects. Her preexisting congenital PPS was worsened by the acquired PPS from sarcoidosis in adulthood, resulting in severe PAH and right-sided heart failure.

PAH is a fatal syndrome with a median life expectancy of 2.8 years without treatment, but early detection and intervention is key for an optimal outcome. SAPH is an important complication in advanced sarcoidosis that can
result in significant morbidity and mortality. Sarcoidosis is a multiorgan noncaseating granulomatous disorder with lung involvement in 90% to 95% of patients. There are multiple pathophysiologies considered in SAPH. These include obliteration of pulmonary vascular bed from chronic hypoxemia and parenchymal lung destruction; granulomatous invasion of pulmonary vessel walls resulting in destruction, remodeling, and subsequent pulmonary veno-occlusive disease-like physiology; vascular remodeling and vasoconstriction from endothelin-induced proliferation of smooth muscle cells and fibroblasts; and physical compression of pulmonary arteries by mediastinal fibrosis or enlarged hilar lymph nodes. With a high degree of clinical suspicion, the confirmatory diagnostic test of choice is RHC, which helps characterize the condition and exclude pulmonary venous hypertension. In addition to treatment of the PAH, treatment of underlying sarcoidosis is required for improved prognosis. PPS is defined as >50% obstruction of tertiary branches from pulmonary trunk. Congenital PPS has been well described in children and is typically associated with a congenital syndrome or heart defect. However, in cases of mild hemodynamic effects, patients don’t present until suprasystemic RVSP. Acquired PPS is a rare disorder, which is often a diagnostic and ther-

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<tr>
<th>Table 1. Catheterization data</th>
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<td>RV pressure</td>
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<td>Pulmonary artery pressure</td>
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<td>Pulmonary capillary wedge pressure</td>
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<td>Pulmonary vascular resistance</td>
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<td>Fick cardiac index</td>
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Figure 4: Cardiac catheterization waveforms. Initial RHC (a); follow-up RHC (b).
peutic challenge. In cases of primary lung disorder with secondary PAH, PPS should be ruled out with a pulmonary angiogram or V/Q scan. PPS pattern on a V/Q scan appears similar to chronic thromboembolic disorders with unmatched segmental defects. However, pulmonary angiogram is the gold standard for diagnosis of PPS, which can also localize the stenosed arteries. Percutaneous angioplasty and stenting are currently the nonsurgical modality of choice in PPS and have shown good prognosis in children. Postsurgical complications include in-stent stenosis occurring years after initial stenting, and stent embolization in cases with severe pulmonary regurgitation. Without considerable reported data or guidelines for adult variant of congenital PPS and acquired PPS, close clinical surveillance is key for positive long-term prognosis and investigation of innovative preventative strategies are warranted.

Teaching Points
1. PPS is typically a congenital disorder that presents in childhood with a congenital murmur and significant PAH.
2. Adult-variant PPS presents itself when the hemodynamic effects from congenital PPS are mild until RVSP is suprasystemic in adulthood. Another pathophysiology for adult-variant PPS involves primary lung pathology causing arterial stenosis.
3. PPS should be considered in adults with insidious onset of dyspnea and chronic thromboembolic pattern on a V/Q scan without hypercoagulable risk factors. This should be carefully worked up given the marked differences in therapy for these disease processes.
4. Pulmonary angiogram is the diagnostic test of choice for PPS.
5. Percutaneous angioplasty and stenting are the nonsurgical treatments of choice for PPS, which require long-term monitoring due to complications of in-stent stenosis and stent embolization.
6. SAPH is an important complication of advanced sarcoidosis with significant morbidity and mortality; treatment should be aimed at both sarcoidosis and PAH.

References
Within the category of idiopathic pulmonary arterial hypertension (IPAH) is a subset of patients who express pulmonary vasoreactivity when challenged at the time of diagnosis with one of several drugs that produce acute vasodilatation. This has become an established hemodynamic marker of response, and is currently advocated in every clinical practice guideline for patients with pulmonary arterial hypertension (PAH).1,2 While vasoreactivity is a continuum rather than an all or none phenomenon, the most commonly used clinical criteria today is a fall in mean pulmonary artery pressure (PAP) of at least 10 mm Hg to a level below 40 mm Hg, with no change or an increase in cardiac output. This definition came from the 1998 World Health Organization (WHO)-sponsored symposium on primary pulmonary hypertension, but was an arbitrary definition and not based on scientific data.3 The long-term effects of treating vasoreactive PAH patients with relatively high doses of calcium channel blockers (CCBs) has resulted in markedly enhanced survival (>20 years for many), with a return to normal or near normal exercise tolerance.4 The biological basis of this subgroup, however, remains uncertain.

In nearly all reported pathologic case series of PAH, varying degrees of medial hypertrophy exist in the pulmonary vasculature, which is interpreted as an expression of underlying vasoconstriction.5 The wide spectrum of responsiveness to vasodilator challenge was thought to be a reflection of the chronicity and the underlying severity of the disease. Although it has not been possible to relate the presence of vasoreactivity specifically to the vascular changes noted on histology, one study reported a qualitative relationship between the patients with more advanced lesions and a reduced likelihood to respond to acute vasodilator testing.6 This study did not clarify whether the presence of vasoreactivity represents a different stage of the disease or a different disease altogether. While it has long been debated whether the favorable response to acute vasodilator challenge and treatment with CCBs identifies a unique subset of patients with IPAH or different stages of IPAH, 3 recent investigations lend additional strong support to the argument that vasoreactive PAH is a distinct phenotype and probably a distinct genotype of PAH.7

Langleben et al7 determined the status of the functional capillary surface area (FCSA) in the lung in patients with IPAH at diagnosis. In the vasoreactive patients, baseline FCSA was normal and increased dramatically during vasodilator challenge. The data support that the increased cardiac output (CO) occurred by true microvascular recruitment and not via distention. The nonreactive IPAH patients had reduced FCSA at baseline, and acute vasodilator testing did not expose more FCSA despite an average 36% increase in CO. This suggests the nonreactive IPAH patients were unable to open occluded arterioles and recruit more downstream capillaries, but rather the increased blood flow simply passes through the remaining patent and already maximally recruited vascular tree.

Next, Halliday et al8 retrospectively evaluated 155 consecutive PAH patients referred for right heart catheterization and acute vasodilator testing. Patients were stratified into 3 categories based on response to acute vasodilator challenge:

a. Classic response: Reduction in mean PAP by >10 mm Hg to a value >40 mm Hg
b. Nonclassic response: Reduction in mean PAP >10 mm Hg but to a value >40 mm Hg
c. Nonresponse: Reduction in mean PAP <10 mm Hg

Consistent with previous reports, 13% of patients demonstrated a classic response to vasoreactivity testing. In the remainder, 8% had a nonclassic response, and 79% of patients were nonresponders. Among the key findings in this study were:

a. Those with a classic response to vasodilator testing had an impressive long-term survival benefit consistent with the original description of this phenomenon,9 whereas there was no survival benefit in those with a nonclassic response compared to nonresponders.

b. Among those with a classic response, 40% had connective tissue disease, yet only IPAH patients demonstrated a survival benefit.
Finally, Hemnes et al.\cite{10} studied the genetic basis of this population using RNA expression patterns in peripheral blood. Microarrays of cultured lymphocytes from vasoreactive and non-vasoreactive PAH patients were performed with quantitative polymerase chain reaction (PCR) done on peripheral blood, and a decision tree was then developed to identify vasoreactive patients. Broad differences in gene expression patterns on microarray analysis were seen including cell-cell adhesion factors, cytoskeletal genes, and rho/GTPase genes. Ten decision trees were built using expression levels of 2 genes as the primary genes: DSG2, (a desmosomal cadherin involved in Wnt/β-catenin signaling), and RHOQ (which encodes a cytoskeletal protein involved in insulin-mediated signaling). These trees correctly identified all vasoreactive patients in a separate validation cohort. This is the first genotype correlation for a phenotypic subset in the history of pulmonary hypertension research.

These important recent contributions to the PAH field provide a compelling argument that vasoreactive PAH is a distinct phenotype and likely a distinct genotype of disease. It also serves as an important reminder to all clinicians and reinforces the published guidelines of the critical importance of acute vasodilator testing in all patients with IPAH to identify this unique subset of patients in whom treatment with CCBs is likely to result in a markedly improved outcome.

References
Circulating Biomarkers in Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension (PAH) is a debilitating vascular disease of the pulmonary circulation that leads to elevation in the pulmonary artery pressure and pulmonary vascular resistance with resultant right ventricular failure and death.\(^1,2\) Despite expanding therapeutic options, PAH continues to have unacceptably high morbidity and mortality.\(^3\) Endothelial cell dysfunction, impaired eicosanoid balance, inflammation, oxidative stress, thrombosis, vascular proliferation, and metabolic dysfunction have all been implicated in the pathogenesis of PAH.\(^1,4\) Early detection, risk assessment, and follow-up for disease progression are essential components of the clinical management of PAH. Currently, treatment decisions are based on assessment of disease severity determined by symptoms and exercise capacity.\(^5\) Unfortunately there is a significant amount of subjectivity and imprecision in these assessments. As a result, there has been increasing interest and research for the identification of useful biomarkers in PAH. The US Food and Drug Administration (FDA) defines a biomarker broadly as a “characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”\(^6\) A valuable biomarker is reproducible, inexpensive, and easy to measure and interpret. While several biomarkers have been proposed for use in PAH, only brain natriuretic peptide (BNP) and N-terminal fragment of proBNP (NT-proBNP) have emerged as recommended biomarkers of dysfunction of the right heart (RV) in PAH, given their stability and relatively long half-life (20 minutes and 1–2 hours, respectively).\(^7,8\) The prognostic significance of BNP was first demonstrated in a study of PAH patients initiated on prostacyclin therapy. In that study, patients with supramedian BNP at baseline (≥150 pg/mL) or after prostacyclin therapy (≥180 pg/mL) had significantly increased mortality.\(^9\) BNP >180 pg/mL was confirmed to be independently associated with mortality in a large US-based registry.\(^10,11\) BNP obtained at or near the time of right heart catheterization (RHC), or at initiation of therapy for PAH reflects invasively determined hemodynamic parameters and markers of exercise capacity including positive correlation with mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), right atrial pressure, and pulmonary vascular resistance (PVR) (PVR).

**Key Words**—right heart failure, endothelial dysfunction, exercise capacity

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BIOMARKERS OF CARDIAC DYSFUNCTION OR OVERLOAD

Brain natriuretic peptide is a peptide hormone produced from cardiac myocytes in response to ventricular stretch due to volume or pressure overload.\(^9\) Previously used as a marker and prognosticator of left ventricular dysfunction, BNP and NT-proBNP have emerged as recommended biomarkers of dysfunction of the right ventricle (RV) in PAH, given their stability and relatively long half-life (20 minutes and 1–2 hours, respectively).\(^10,11\) The prognostic significance of BNP was first demonstrated in a study of PAH patients initiated on prostacyclin therapy. In that study, patients with supramedian BNP at baseline (≥150 pg/mL) or after prostacyclin therapy (≥180 pg/mL) had significantly increased mortality.\(^12\) BNP >180 pg/mL was confirmed to be independently associated with mortality in a large US-based registry.\(^13\) BNP obtained at or near the time of right heart catheterization (RHC), or at initiation of therapy for PAH reflects invasively determined hemodynamic parameters and markers of exercise capacity including positive correlation with mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), right atrial pressure, and pulmonary vascular resistance (PVR) (PVR).
pressure (RAP), and World Health Organization (WHO) functional classification; and negative correlation with cardiac index (CI), maximal oxygen consumption (VO₂ max), and 6-minute walk distance (6MWD).¹¹,¹⁴ Similar to BNP, NT-proBNP correlates with contemporaneously measured hemodynamics and mortality in PAH.¹⁵⁻¹⁹ Serum NT-proBNP ≥ 1400 ng/mL was associated with reduced survival and observed in 10 of 32 patients with PAH (31%) in one study.¹⁶ BNP and NT-proBNP are also useful as a serially obtained marker of response to therapy and progression of disease. Change in BNP during the course of therapy has been shown to correlate with change in WHO functional classification, 6MWD, and pulmonary hemodynamics.²⁰ More compelling are several studies demonstrating that, compared to an increase, a decrease in BNP or NT-proBNP during therapy is associated with improved survival.¹² These data support the use of BNP or NT-proBNP as a biomarker of hemodynamic and clinical severity of disease at therapy initiation, as well as serial change in BNP in assessment of risk of progression despite PAH-directed therapy. However, measurement and interpretation of natriuretic peptide levels have limitations. For example, BNP and NT-proBNP are affected by impaired renal function, obesity, age, and gender.²¹⁻²⁴

Detectable plasma levels of cardiac-specific troponin proteins are an indicator of myocardial injury, and the use of this biomarker—both its presence and degree of elevation—is well established in the evaluation of acute coronary syndromes and left-sided heart failure. In PAH, detectable circulating cardiac troponin T is associated with RV dysfunction and lower mixed venous oxygen saturation (MVO₂), 6MWD, and survival.²⁵⁻²⁷ There are far fewer studies of cardiac troponin T than the natriuretic peptides for risk stratification in PAH, but the studies available demonstrate close association of the two markers. One recent study supports utilizing highly sensitive cardiac troponin T in addition to BNP, although the incremental improvement in predictive ability was small and the number of patients studied was low. The wide-

### Table 1.

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<thead>
<tr>
<th>Biomarker</th>
<th>Cellular Pathways</th>
<th>Associations</th>
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<tr>
<td>Brain natriuretic peptide</td>
<td>Marker of myocardial stretch</td>
<td>Mortality, hemodynamic measurements (RAP, mPAP, PVR, CI, 6MWD)</td>
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<td>Cardiac troponin isofroms</td>
<td>Marker of cardiac injury</td>
<td>Mortality, BNP/NT-pro-BNP and 6MWD</td>
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<td><strong>Related to vascular endothelial dysfunction</strong></td>
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<tr>
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<td>Potent vasoconstrictor</td>
<td>Mortality, hemodynamic measurements (mPAP, PVR, CI, 6MWD)</td>
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<td>von Willebrand factor</td>
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<td>Mortality</td>
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<td>Endostatin</td>
<td>Anti-angiogenic factor</td>
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<td>Circulating endothelial cells</td>
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<td>Pentraxin</td>
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<td><strong>Related to systemic inflammation or oxidative injury</strong></td>
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<td>Interleukins, especially interleukin-6</td>
<td>Inflammatory mediators</td>
<td>Mortality, quality of life</td>
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<td>Osteopontin</td>
<td>Mediates cell migration, adhesion, remodeling and survival of vascular cells</td>
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<td>Isoprostanones</td>
<td>Marker of lipid peroxidation of arachidonic acid</td>
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<td>High density lipoprotein</td>
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RAP = Right atrial pressure; mPAP = Mean pulmonary artery pressure; PVR = Pulmonary vascular resistance; 6MWD = Six-minute walk distance; CI = Cardiac index; SvO₂ = Mixed venous saturation.
spread use of troponin T has been limited due to its lack of specificity, as troponin T levels are elevated in other conditions including acute coronary syndrome, left ventricular dysfunction, renal insufficiency, and pulmonary embolism. In addition, different cardiac troponin isoforms and assays may have differing predictive ability, as has been previously demonstrated. Clinical availability of different troponin isoform assays (including standard- and high-sensitivity assays) may be a limitation in widespread clinical use.

**BIOMARKERS OF VASCULAR AND ENDOTHELIAL DYSFUNCTION**

Endothelin-1 (ET-1) is a peptide found in abundance in the human lung and, through action of endothelin receptors (ETA and ETB) on vascular smooth muscle cells, is implicated in the pathogenesis of PAH. Endothelin receptor antagonists are approved for the treatment of PAH. Levels of circulating ET-1 and related molecules are logical biomarkers of interest in PAH. ET-1 is elevated in PAH compared to controls, and correlates with pulmonary hemodynamic parameters. In addition, higher ET-1 levels are associated with increased mortality in patients treated for PAH. ET-1’s precursor, big-ET-1, has a longer half-life and hence is more stable than ET-1. In a small study of PAH patients, big ET-1 was strongly correlated with pulmonary hemodynamics including PVR, mPAP, and CI, as well as 6MWD. Carboxy-terminal pro-endothelin-1 (CT-pro-ET-1) is derived from the ET-1 propeptide in equal amounts as ET-1, and has recently been investigated as a potential biomarker in PAH. In a small study of PAH patients, patients in whom the composite endpoint of clinical worsening, lung transplantation, or death occurred had higher levels of CT-pro-ET-1 after multivariate adjustment for other biomarker levels (NT-proBNP, troponin I, and others). Despite promising associations between these potential mediators and outcomes in PAH, several limitations have prevented them from adoption into mainstream clinical practice. None of these associations have been validated longitudinally, and the effects of PAH-approved therapies are unpredictable. While some of the studies above included patients on various PAH-approved agents, other studies show ET-1 levels rise,6,39 are unchanged,40 or are lower41,42 depending on the agent used. Moreover, ET-1 level varies with race, age, gender, and certain medications including statins and beta-blockers, which makes it difficult to determine meaningful cutoff values.43

Von Willebrand factor (vWF) is a large glycoprotein produced in endothelial cells and megakaryocytes that plays a significant role in clot formation and platelet recruitment. Elevated plasma levels of vWF are another indicator of endothelial dysfunction and are found in multiple cardiovascular diseases, particularly valvular disease. Higher vWF level has been reported in patients with PAH compared to other forms of pulmonary hypertension (PH) and is associated with increased mortality. Angiopoietin-1 (Ang-1) is an angiogenic factor that binds receptor tyrosine kinase TIE2 on endothelial cells and is necessary for vascular formation. Ang-1 and its competitive inhibitor for TIE2 binding, Angiopoietin-2 (Ang-2), have been implicated in the pathogenesis of PAH. In a study of patients with idiopathic PAH, plasma levels of Ang-1 and Ang-2 were higher in PAH patients compared to healthy controls. Moreover, higher plasma levels of Ang-2 were associated with lower CI and mixed venous oxygen saturation (SvO2) and higher PVR, and, with therapy initiation, changes in Ang-2 correlated with changes in hemodynamics. Further studies of Ang-2 as a possible biomarker of PAH are warranted.

Like Ang-2, endostatin is an angiogenic peptide. It is synthesized by myocardium, is detectable in the peripheral circulation of patients with decompensated heart failure, and predicts mortality.48 In PAH, reduced RV myocardial oxygen delivery is felt to contribute to a transition from RV adaptation to failure. Elevated levels of endostatin have been documented in the serum of patients with PAH and correlate with disease severity, RV dysfunction, and mortality. Whether the level changes with response to therapy or provides additional prognostic or physiologic insight beyond BNP is uncertain.

Free circulating endothelial cells (CECs) have been detected in states of vascular damage, remodeling, and dysfunction. The number of CECs measured by flow cytometry has been shown to be higher in patients with PAH as compared to healthy controls or those with chronic thromboembolic pulmonary hypertension (CTEPH) and correlated with pulmonary artery pressure. In a separate study of children with PAH, the number of CECs decreased after PAH-targeted therapy initiation, suggesting a correlation with response to treatment. In fact, an increase in the number of CECs preceded clinical deterioration. These results are promising; however, they need to be validated longitudinally and in larger cohorts. In addition, the wide differences in the methodology and the availability of techniques to measure CECs may not be ready for clinical use.

Impaired nitric oxide production has long been implicated in the pathogenesis of PAH and is another marker of endothelial dysfunction. While more difficult to measure in the serum, levels of exhaled nitric oxide (eNO) have been explored in patients with PAH, but results have been mixed. Treatment with prostacyclin therapy or bosentan has been demonstrated to increase the level of eNO, but whether the presence or magnitude of an increase translates to beneficial outcomes is uncertain.

Cyclic guanosine monophosphate (cGMP) is an intracellular second messenger of nitric oxide and an indirect marker of natriuretic peptide production. Urinary and plasma cGMP have been shown to be elevated in PAH (compared to controls), and urinary cGMP correlates inversely with CI and SvO2. The response of plasma cGMP to PAH-specific therapy has been variable. One study of PAH patients showed that cGMP levels decreased by 30% following inhaled iloprost administration. Another study
examined the response of cGMP levels to the administration of oral sildenafil and inhaled nitric oxide, and found that combination treatment yielded the greatest increase in blood cGMP levels in patients with PAH.62

Human pentraxin 3 (PTX3) is a protein synthesized by vascular cells that regulates angiogenesis, inflammation, and cell proliferation.63 In a study of PAH patients (idiopathic and connective-tissue disease-related), PTX3 level was significantly elevated in PAH patients compared to controls and more prominently in the connective-tissue disease-related PAH.64 Confirmation of these findings in other cohorts of patients with PAH and determination of PTX3 levels in patients with connective tissue disease without PAH are needed.

BIOMARKERS RELATED TO COLLAGEN METABOLISM

The main feature of vascular remodeling seen in PAH is collagen deposition in the remodeled pulmonary vessels. The best way to quantify collagen deposition in the pulmonary vasculature is by tissue analysis at autopsy or of explanted lungs. Antemortem assessment of collagen in the pulmonary vasculature is not possible with current imaging techniques, nor is lung biopsy considered safe. Several studies suggest that ongoing collagen metabolism in the pulmonary vasculature can be assessed by measuring circulating levels of collagen metabolites. A recently published study by Safdar et al showed that circulating levels of N-terminal propeptide of procollagen III (PIIINP), carboxy-terminal telopeptide of collagen I (CITP), matrix metalloproteinase-9 (MMP-9), and tissue inhibitor of metalloproteinase I (TIMP-1) were elevated in PAH patients as compared to age- and gender-matched healthy controls.65 In particular, PIIINP levels increased with PAH disease severity, and there was a trend toward worse outcome in terms of mortality and lung transplantation in patients with higher PIIINP tertiles. In another study, elevated PIIINP levels further associated with worse indices of quality of life domains such as the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), Minnesota Living With Heart Failure (MLWHF) physical, and EuroQOL 5 dimensions questionnaire (EQ-5D).66 In addition, PIIINP showed good predictive capabilities with respect to the levels of RAP, and worsening WHO functional class and 6MWD, all of which are widely accepted parameters of PAH severity.100

BIOMARKERS RELATED TO SYSTEMIC INFLAMMATION AND/OR OXIDATIVE INJURY

Inflammation is thought to play a key role in the pathogenesis of PAH, and several inflammatory markers have been found to be elevated in plasma of PAH patients including multiple interleukins: IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, and IL-12p70.57,68 IL-6 in particular has been shown to correlate with mortality,68,69 and a recent study demonstrated an association with quality of life domains in patients with PAH.70 Not all studies replicate these findings.71

Osteopontin (OPN) is a matricellular protein that mediates cell migration, adhesion, remodeling, and survival of the vascular and inflammatory cells and has been investigated as a biomarker in experimental PH and in human disease. In a study of idiopathic PAH patients, OPN levels measured at the time of the diagnostic RHC were elevated as compared to controls and OPN levels correlated with RAP, WHO functional classification, and 6MWD. Moreover, in multivariate analysis, OPN was found to be an independent predictor of mortality in idiopathic PAH patients.72 F2-isoprostone is a marker of lipid peroxidation of arachidonic acid, which stimulates endothelial cell proliferation and ET-1 synthesis and may play a role in the pathogenesis of PAH.73 Urinary F2-isoprostone, when measured at the time of diagnosis, has been shown to be an independent predictor of mortality in a cohort of incident PAH patients.74 In patients with idiopathic PAH, plasma concentration of 15-F2t-isoprostane is elevated as compared to controls and is independently associated with mortality.75

BIOMARKERS RELATED TO NON-CARDIOPULMONARY ORGAN DYSFUNCTION

The presence of comorbidities increases morbidity and mortality in PAH. The most consistently demonstrated effect has been that of renal failure. As a possible prognostic biomarker, elevated serum creatinine has been associated with higher RAP and lower CI and is an independent predictor of mortality in patients with PAH.76,77 A large prospective observational registry reported that renal dysfunction was associated with mortality in PAH, but did not utilize quantifiable markers of kidney function.13

A marker of combined cardiac and renal dysfunction, hyponatremia has been demonstrated to be present in patients with left-sided heart failure. Hyponatremia as defined by a decreased serum sodium concentration ≤136 mEq/L, and is associated with RV dysfunction and hemodynamics in patients with PAH.78 Hyponatremia has also been independently associated with increased mortality in patients with PAH.78,79

The red cell distribution of width (RDW) is routinely measured via the complete blood count and reflects the variability in the size of circulating red blood cells. Increased RDW was found to be independently associated with increased mortality in a cohort of mixed PH cases, including PAH patients.80 In another study of idiopathic PAH patients, RDW was again found to be prognostically significant and added significant value to the measurement of NT-proBNP and exercise capacity.81 Several mechanisms have been proposed linking pulmonary vascular disease and increased RDW; however, none has been definitively demonstrated.

BIOMARKERS RELATED TO OTHER NOTABLE PROCESSES

Circulating fibrocytes are bone marrow-derived cells (CD45+/collagen I+) that contribute to organ fibrosis and extracellular matrix deposition.82 Experimental hypoxia-induced PH models have suggested a role for circulating fibrocytes in the development of vascular remodeling. In a study of mice, administration of continuous treprostinil infusion
significantly inhibited the recruitment of these cells into the remodelled pulmonary vessel walls and reduced RV systolic pressure. In a study of children and young adults with PAH, patients with PAH were found to have higher number and percentage of circulating fibrocytes as compared to controls and the number of fibrocytes correlated with mPAP. Like CECs, broad application of an analytical method that relies on flow sorting of live cells is unlikely due to multiple limitations including issues with specimen handling, required technical expertise and equipment, and cost.

MicroRNAs (miR) are a group of noncoding RNAs 18 to 25 nucleotides in length that regulate about 30% to 60% of the human genome. Several miRs have been implicated in the pathogenesis of PAH including miR-150, miR-17-92, miR-21, and miR-204. Circulating miRs are highly stable and protected from RNase digestion; therefore, they may have a potential role as biomarkers for PAH. The levels of multiple circulating miRs have been shown to be differentially expressed in patients with PAH compared to healthy controls. miR-26a, miR-204, and miR-150 are all known to be reduced in patients with PAH. Reduced levels of miR-150 were associated with 6MWD and WHO functional classification, and have been shown to be an independent risk factor for mortality in PAH.

Nucleic acid amplification techniques are now more readily available for clinical testing. Unfortunately, the level of various miRs in a healthy population, effects of other related and unrelated disease states, and effects of therapy are uncertain at this time. Further study and validation may allow miRs to be a promising biomarker in multiple cardiovascular diseases including PAH.

There are new data suggesting a connection between metabolic dysfunction and PAH. In a cohort of incident PAH patients, mean hemoglobin A1c was elevated in patients with PAH as compared to age-matched nondiabetic controls and was an independent predictor of mortality. In addition, high-density lipoprotein (HDL) cholesterol is a marker of vascular health and is affected by insulin resistance. In a study of PAH patients, HDL levels were lower in PAH patients as compared to controls, and higher HDL levels were associated with decreased mortality.

Serum HDL levels were positively correlated with CI and negatively correlated with PVR. These findings could not be confirmed in a separate study of incident PAH patients.

CONCLUSION
Pulmonary arterial hypertension is associated with increased morbidity and mortality. Early detection and treatment have improved outcomes. Biomarkers are needed to help identify patients early, risk classify them, and evaluate their response to treatment. Presently, natriuretic peptides have demonstrated utility in assessing disease severity at diagnosis and during the course of the disease, as well as a marker of treatment response. Despite many other substances being investigated as potential biomarkers in PAH, more research is needed to validate the results of small studies and assess their clinical utility. Widespread clinical use of current investigational biomarkers will require validated clinical laboratory techniques and increased knowledge of levels in the healthy population as well as other disease states.

Nonetheless, biomarkers are a promising means of improving our ability to differentiate PAH from other related diseases, assess treatment response, and identify patients at high risk of disease progression or death from PAH, and thus ongoing studies are warranted.

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Pulmonary arterial hypertension (PAH) is a progressive, often lethal condition characterized by pulmonary vascular remodeling, pathologic rise in right ventricular (RV) afterload, and increase in pulmonary artery (PA) pressures.\(^1\)\(^-\)\(^3\) Though PAH is a disease originating in the pulmonary arteriolar tree, it is typically also manifested in stereotypical changes in the RV, which is normally morphologically smaller and thinner-walled than the left ventricle (LV), in keeping with its design to deliver blood flow through a low-resistance pulmonary circuit.

However, as pulmonary vascular resistance (PVR) increases, RV hypertrophy, RV dilatation, and ultimately RV dysfunction occur.\(^4\)\(^-\)\(^5\) Indeed, RV dysfunction is an important mediator of patient symptoms in PAH, and RV failure is the most common cause of mortality in PAH patients.\(^6\)\(^-\)\(^7\)

Because of the physiologic importance of the RV, RV imaging is critical in the initial diagnostic evaluation and serial assessment of PAH patients, and can provide indirect insight into the status of the disease at the level of the pulmonary vasculature. Moreover, newer therapies for the treatment of patients with PAH are now being investigated, which may directly impact RV function, rather than solely causing pulmonary vasodilatation.\(^8\)

Despite this critical role in the pathophysiology of PAH, imaging assessment of RV structure and function has infrequently been used as a primary endpoint in large, randomized clinical trials of PAH therapeutic agents, and controversy still exists as to the most appropriate method of RV imaging in both clinical and research settings.

Two-dimensional (2D-TTE) and Doppler transthoracic echocardiography (DE) has been a mainstay of the clinical assessment of patients with PAH. However, due to the complex 3-dimensional geometry of the RV, an accurate assessment of RV volumes and ejection fraction (EF) has been challenging to obtain via traditional 2D-TTE.\(^9\) However, echocardiography is inexpensive, widely available, and can provide important hemodynamic information via Doppler.

Cardiac magnetic resonance imaging (CMR) has been considered the gold standard for imaging of the RV due to its ability to provide accurate RV volumes, right ventricular ejection fraction (RVEF), and to simultaneously evaluate for evidence of congenital heart disease and shunts.\(^10\) Challenges with CMR have included requirement for breath holding, lack of widespread availability, expense associated with magnetic resonance imaging (MRI) equipment, and issues with noncompatible implanted devices and claustrophobia. Over the past decade, there have been dramatic advances in 2D-TTE, 3-dimensional echocardiographic (3D-TTE) technology, and increased understanding of the prognostic significance of existing surrogates of RV function by echocardiography. Similarly, CMR technology has continually evolved to allow faster acquisition, tissue characterization, and flow dynamics.

The question remains as to whether these technological advances have shifted the debate toward which modality is optimal both for routine clinical practice and for a possible surrogate endpoint in PAH clinical trials. This debate forms the topic of this article.
ECHOCARDIOGRAPHY:
FOUNDATION FOR RV ASSESSMENT IN CLINICAL PRACTICE AND PAH CLINICAL TRIALS

Doppler echocardiography and 2D-TTE is frequently the first diagnostic test employed in the evaluation of patients with known or suspected PAH, in part because of its widespread availability, ease and speed of image acquisition, lack of ionizing radiation, and because patients with what may ultimately prove to be PAH are often initially referred for evaluation of unexplained dyspnea. Echocardiography also has the advantage of providing hemodynamic evaluation such as an estimate of PA pressures and LV filling pressure, and the ability to evaluate for valvular heart disease and LV systolic and diastolic dysfunction.4,11,12

Traditional 2D-TTE has been more limited in terms of the assessment of RV structure and function in part because of the triangular, crescentic geometry of the RV, which is difficult to image from a single echocardiographic view and makes volumetric assumptions used in quantitative assessment of left ventricular ejection fraction (LVEF) untenable for calculating RVEF.13 However, despite the inability of 2D-TTE to provide RV volumes and RVEF, a number of surrogates of RVEF have been developed and validated using 2D, M-mode, and tissue Doppler.

NEW EVIDENCE AND APPLICATIONS FOR EXISTING SURROGATES OF RV STRUCTURE AND FUNCTION

2D-TTE assessments of RV function have generally used single-plane measurements acquired from the apical 4-chamber view. Several of these measurements rely on the unique contractile pattern of the RV, in which the majority of global RV contraction occurs in the longitudinal axis vs the transverse axis in both the normal RV and in patients with PAH.14

Tricuspid annular plane systolic excursion (TAPSE) is perhaps the most common of these surrogates, obtained by measuring the displacement of the lateral tricuspid annulus between systole and diastole either by M-mode or 2D-TTE. The great advantage of TAPSE is that it is very simple to acquire, does not require specialized equipment or high endocardial definition, and is easily reproducible.13,15 TAPSE has proven to be a useful measurement that has correlated well with RVEF by radionuclide angiography and 3D-TTE.15,16 In the past decade, TAPSE has also been shown to correlate well with invasive hemodynamic variables such as cardiac index and clinical outcomes such as survival in patients with PAH.17,18 Low TAPSE values have correlated with lower stroke volume index and have been associated with higher transplant free mortality.19

Similar to TAPSE, tissue Doppler peak systolic velocity of the lateral tricuspid annulus (TD S') is another measure of longitudinal contraction of the RV, which, as the nomenclature implies, uses tissue Doppler rather than M-mode or 2D. A TD S' velocity of less than 10 cm/s is suggestive of RV dysfunction,20 and low TD S' velocities are associated with a reduced cardiac index 21 and correlate with invasively derived stroke volume index.2,22 While these longitudinal measures of RV function have been increasingly validated in the last decade, some of their limitations have also become apparent. TAPSE has not correlated well with RVFAC in patients with repaired congenital heart disease,23 and the reason for this observation may be that post cardiac surgery, there is a fundamental change in the global contractile pattern of the RV, with greater proportion of contraction in the transverse axis and lower TAPSE values overall.24

Right ventricular fractional area change (RVFAC) may prove a better surrogate of RV function in the post cardiac surgery patients, because it incorporates both longitudinal and transverse components of RV contraction into a single measurement. RVFAC is defined as the ratio of end-diastolic area minus end-systolic area divided by end-diastolic area obtained from the apical 4-chamber view. RVFAC of less than 36% is defined as RV dysfunction.9

Though RVFAC has many of its own limitations, when measured carefully, it correlates well with RVEF and global RV function.25,26 The major disadvantage of RVFAC is that it requires superior endocardial definition compared to TAPSE and TD S' to allow the reader to delineate both systolic and diastolic areas appropriately, and can have greater variability based on the imaging alignment used to optimize the 2D-TTE image as well as due to subjective assessment of where the endocardium is defined. As a result, the measurement of RVFAC is typically less reproducible than TAPSE and TD S' in clinical practice.

The last DE measurement of RV function commonly employed in PAH patients is the RV myocardial performance index (MPI) or Tei index. This can be measured using either pulse wave Doppler or (in the current era) more frequently with tissue Doppler; the latter is defined as the sum of isovolumetric contraction time and isovolumetric relaxation time divided by RV ejection time. MPI is a combined measurement of both RV systolic and diastolic function and has the potential advantage of being relatively independent of heart rate, loading conditions, and tricuspid regurgitation.9,27 The MPI has correlated well with clinical and hemodynamic variables such as cardiac index and PA pressures in PAH and chronic thromboembolic pulmonary hypertension (PH), has been predictive of survival, and has been used as an outcome measure in previous studies of PAH therapy.28-30

Current guidelines suggest the use of 2 or more quantitative metrics of RV function in patients with PH and/or RV dysfunction,9 and as a result, TAPSE, TD S', and RVFAC form the basis for quantitative assessment of RV function in many PAH centers, whereas MPI is more commonly used in research settings as its calculation is somewhat cumbersome. However, these metrics are now being supplemented by newer measurements, including noninvasive estimates of PVR, RV strain imaging, and 3D assessment of RV volumes and RVEF.

NEWER DEVELOPMENTS IN ECHOCARDIOGRAPHIC IMAGING OF THE RV
Noninvasive Estimates of PVR

An accurate and simple noninvasive measurement of PVR is one of the "holy
grails” of the noninvasive assessment of the RV in PAH, because conventionally this information could only be provided by catheterization, and knowledge of PVR might prove extremely valuable to helping clinicians better phenotype patients with known or suspected PH. Two broad approaches have been employed in terms of the echocardiographic estimation of PVR, the first being fully quantitative and providing an exact PVR estimate via a formula for PVR, while the second has been semi-quantitative, providing an estimated range of PVR.

The fully quantitative measures of PVR have sought to mimic the catheterization-based PVR calculation by dividing an estimate of transpulmonary pressure gradient, typically based on tricuspid regurgitant jet velocity, by an estimate of RV stroke volume or PA flow. Abbas et al published the first such formula, which was reasonably accurate when compared to invasively derived PVR at relatively low PVR, but was less reliable at higher PVR. Moreover, this formula was inherently a measure of total pulmonary resistance rather than PVR per se, as it did not include a measure of left atrial pressure in the calculation. This element was incorporated by a revised formula developed by Dahiya and Marwick using the pulse wave/tissue Doppler E/E’ ratio as a left atrial pressure estimate: PVR = (pulmonary artery systolic pressure [PASP] – E/E’)/right ventricular outflow tract (RVOT) velocity time integral (VTI). This formula was subsequently validated in a cohort of PAH patients with a broader range of PVR values including at high PVR.

An alternative approach to this fully quantitative assessment has been a semi-quantitative method evaluating the pulse wave Doppler profile in the RVOT. In patients with pulmonary vascular disease, the normally smooth and parabolic RVOT pulse wave Doppler envelope becomes notched, presumably due to wave reflection from the incident wave of ejected blood against the stiff, non-compliant pulmonary vascular tree. The stiffer and more noncompliant the pulmonary vasculature, the earlier the reflected wave returns, causing the notch to fall earlier in the RVOT pulse wave Doppler profile. In their study, Arkles et al demonstrated that PAH patients with a mid-systolic notch typically had PVR >5 Wood units.

In an attempt to combine both of these approaches, Opotowski et al incorporated the presence of Doppler notching in the RVOT into a revised fully quantitative equation to estimated PVR: (PVR = (PASP/RVOT VTI) + 3 if notch present). This was validated in a larger cohort of patients with PAH and correlated with invasively derived PVR better than the Abbas formula across PVR values.

**RV Strain Imaging**

More recently, strain imaging, which measures the deformation of myocardial tissue rather than translational motion, has been applied to imaging of the RV using both tissue Doppler imaging as well as newer speckle-tracking technology. RV strain imaging can be obtained as global and regional longitudinal strain, as well as radial and circumferential strain, though in practice RV longitudinal strain is most commonly reported. The advantage of strain and strain rate imaging over other contemporary methods to assess RV function is that it is less influenced by translational motion of the RV than other metrics such as TAPSE, may be more sensitive for detecting early RV dysfunction, and can provide information regarding regional variations in RV function Figure 1).

RV global longitudinal strain has correlated well with invasive hemodynamic variables, has been associated with survival in patients with PAH, and overall may be more accurate as a measure of global RV function than traditional longitudinal measurements. RV strain does have some important limitations in that, similar to RVFAC, it is somewhat dependent on endocardial definition to provide accurate speckle tracking of the RV septum and free wall. Strain imaging is also somewhat variable based on the ultrasound equipment used to acquire images and the specific vendor, although vendor-independent platforms have also been developed recently. Lastly, there is a relative paucity of normative data for strain imaging in the RV. Nevertheless, RV strain imaging is gaining greater traction.
in both clinical and research settings as a measure of RV function in PAH patients, and is likely to be at least one imaging endpoint in future PAH clinical trials.

Real-Time 3D Echocardiographic Imaging

With continued advancement in ultrasound technology, 3D imaging of the RV has become increasingly employed. This had initially required a full volume acquisition of the RV, typically from the apical 4-chamber view over several beats, with breath holding and a summation method of discs to reconstruct RV volumes. Challenges in 3D imaging include limited spatial and temporal resolution, and the difficulty in imaging the entire RV from a single echocardiographic view, especially with a very dilated RV, which is often seen in PAH. In addition, offline reconstruction of the RV to render RV volumes and EF could be quite time-consuming, and artifacts could be introduced due to motion over a breath hold. The major advantage, however, is that 3D-TTE could provide an estimate of RV volumes and RVEF, and can supplement the 2D and DE assessment in select patients.

A variety of small clinical studies have demonstrated that RV volumes and RVEF by 3D-TTE have good agreement with those generated by CMR, although 3D-TTE tended to slightly underestimate RV volumes. Newer 3D-TTE systems now permit the acquisition of 3D RV volumes in real time over a single beat, speeding up acquisition and reducing the likelihood of artifacts introduced over several beats of acquisition. Single-beat 3D-TTE has proven feasible—obtainable in 96% of patients in a small study of PAH patients, and again has shown good agreement with CMR volumes with tendency to slightly underestimate stroke volume and RVEF.

Knowledge-Based 3D Reconstruction of the RV From 2D Anatomical Landmarks: The Ventripoint System

Some of the disadvantages of traditional 3D-TTE imaging might be overcome by use of a newer technology termed knowledge-based reconstruction. This utilizes a knowledge database of RV geometry in PAH to interpolate RV contours between known anatomical landmarks such as the RV apex, septum, tricuspid and pulmonic annulus. Using a proprietary probe and reconstruction software, this technology allows for rapid 3D reconstruction of RV volumes and RVEF from standard 2D-TTE images (Figure 2), without the requirement for imaging the entire RV in a single view. This technology was first evaluated in a small cohort of patients with repaired Tetralogy of Fallot in comparison to CMR, and showed similar RV volumes and EF. Knowledge-based reconstruction was then studied in 27 patients with PAH in comparison to CMR, and the 3D-TTE volumes correlated well with CMR, but in contrast to traditional 3D-TTE, RV volumes were slightly higher using knowledge-based reconstruction vs CMR.

The commercial application of this technology is the Ventripoint imaging system, which was evaluated in a multicenter clinical trial in PAH patients in comparison to CMR. Though full results of the study have not been published to date, the Ventripoint system reportedly generated similar volumes to...
CMR performed within 24 hours of the Ventripoint echocardiogram, and based on the results of this trial data, the Ventripoint system has been approved by the United States Food and Drug Administration for RV quantification. To date there has been relatively little clinical experience with this technology in PAH patients outside of the clinical trial arena, but this system certainly has the potential to significantly enhance routine echocardiographic assessment of RV volume and EF. Using the Ventripoint technology might be a less costly secondary endpoint in future PAH clinical trials.

CMR Should Be Utilized in Both Clinical Practice and PAH Clinical Trials

To advance the field of PAH, imaging must offer more than a simple, subjective evaluation of RV size and function. CMR, with its 3D capabilities and tissue characterization techniques, not only provides accurate diagnostic information, but data obtained from CMR can be used for risk stratification purposes and for gauging treatment response. In addition, CMR can provide substantial mechanistic insight into this disease so that therapy can be targeted more effectively.

ASSESSMENT OF RV MASS, VOLUME, AND FUNCTION IS BEST PERFORMED BY CMR

CMR is the gold standard for assessment of RV mass, volume, and function.58,49 No other noninvasive technique can provide accurate and reproducible measurements of these parameters without any radiation or contrast exposure. In 64 patients with PAH, decreased stroke volume index and RV end-diastolic volume index by CMR were significantly associated with poor outcomes.50 The statistical significance for RV end-diastolic volume was even greater when corrected for age, gender, and body surface area.51 In a separate study evaluating 110 patients with incident PAH, both a decrease in RVEF at baseline and a change in RVEF by only 5% over 12 months were associated with poor survival in a multivariate analysis.52

In an effort to overcome the 2D limitations of echocardiography, 3D-TTE was developed to measure RV volumes and function. Feasibility and reproducibility have been studied in normal and abnormal right ventricles, but there are very little data in patients with PAH. In addition, 3D-TTE tends to underestimate RV volumes compared to CMR even in healthy hearts.53 Despite technological advances in the last 3-5 years, offline analysis remains time-consuming, and expertise is needed to acquire the appropriate 2D image. Furthermore, CMR appears to be more cost effective in detecting incremental changes in RVEF and RV end-diastolic volume—an attractive quality when considering imaging modalities for clinical trials.54 Few of the pivotal trials for current PAH therapies examined imaging parameter changes, but several smaller studies found significant changes in CMR-derived mass, volume, and RVEF with these medications.55-59 2DE-derived parameters have also been explored as potential endpoints, but the superior accuracy, reliability, and reproducibility of CMR makes it ideal for clinical studies. Recently, the EURO-MR study showed significant changes in CMR indices of RV function and 6-minute walk distance after 12 months of PH-directed therapy.60 Although future PAH-therapy trials should include CMR parameters for greater insight into how these drugs work, the clinical relevance of a change in these measurements must be established before they can be considered true clinical endpoints.

NEWER DEVELOPMENTS IN CMR IMAGING OF THE RV

RV Strain Imaging

One of the most promising novel imaging techniques is RV myocardial strain. Strain is a measure of myocardial deformation and is calculated as the percentage change in length of the myocardium during relaxation and contraction. Strain can be measured in the longitudinal, circumferential, and radial directions. For RV strain, global longitudinal strain, which averages the peak systolic strain throughout the RV myocardium, is the most commonly reported parameter.

A variety of CMR methods, many based on conventional tagging techniques, have been used to calculate myocardial deformation of the RV. Recently, multimodality tissue tracking of the RV has been shown to correlate well with other CMR strain techniques as well as RVEF, and can be applied retrospectively to standard cine images.61 While 2DE-derived RV strain has the potential to provide a more accurate assessment of RV function compared to conventional 2D-TTE parameters, CMR-derived RV strain may shed additional light on the mechanism by which the RV becomes dysfunctional. For example, little data exist regarding RV circumferential strain because short-axis images of the RV with 2D-TTE are difficult to obtain for speckle-tracking analysis. CMR, due to its multiplanar capabilities and improved spatial resolution, can easily measure this variable. This parameter is potentially important, as Kind et al showed that transverse wall motion of the RV might be a better reflection of RV function than longitudinal wall motion.62,63

In addition, while regional RV longitudinal strain is highly variable by 2D-TTE and rarely reported, regional strain by CMR is more feasible, reliable, and may detect changes in RV structure prior to a decrease in RVEF.64,65 Although not yet studied in the RV, changes in regional tissue velocities by CMR-derived tissue phase mapping might also identify early myocardial disease before a decline in ventricular function is detected.66

Delayed Contrast Enhancement and T1 Mapping Imaging

A great strength of CMR is its ability to characterize tissue and detect abnormal areas of myocardium. Not only does RV dysfunction play a key role in the pathophysiology of PAH, but, in one study, an RVEF less than 35% was better than PVR at predicting adverse outcomes.52 This suggests that there are changes within the RV myocardium itself that contribute significantly to the overall disease process.

Delayed contrast enhancement of the RV insertion points is a common finding in PAH patients and reflects either
fibrosis or myocardial fiber disarray in this region of the heart. Multiple publications have explored the clinical significance of this finding.67-70 Although the existence and extent of delayed enhancement consistently correlates with increased RV mass, volumes, and PA pressure, it does not appear to independently predict outcomes.71-73

While delayed contrast enhancement identifies regional myocardial abnormalities, a recently developed MRI technique, T1 mapping, allows quantification of diffuse myocardial fibrosis with or without the use of contrast.74-78 A recent paper showed a strong correlation between T1 mapping values of the RV insertion points and indices of RV dysfunction.79 However, a better use of T1 mapping might be the detection of diffuse interstitial fibrosis in the RV.80 Higher resolution sequences, which are required for the thin-walled RV myocardium, are in development and show promise for fibrosis quantification (Figure 3). Detection of fibrosis within the RV myocardium may serve as a therapeutic target for future PAH therapies.

**RV Perfusion Imaging**

A critical component of RV failure is a decline in coronary perfusion of the RV and subsequent RV ischemia. 2D-TTE, while standard for assessing wall motion abnormalities of the LV, cannot evaluate RV perfusion. However, myocardial perfusion reserve can be evaluated by CMR using contrast and a vasodilator such as adenosine or regadenoson. In a small study of 25 patients referred for PAH evaluation, the myocardial perfusion reserve index for both LV and RV were significantly decreased compared to controls.81 Furthermore, a decrease in RV myocardial reserve index significantly correlated with a decline in RV workload and RVEF. Similar to markers of fibrosis, RV MPI may also be used as a measure for the effectiveness of PAH therapies.

**Pulmonary Vasculature Imaging**

While the RV plays a key role in the pathophysiology of PAH, its function is strongly affected by the pressure and resistance within the pulmonary vasculature. Both 2D-TTE and CMR can evaluate pulmonary vasculature hemodynamics with Doppler and velocity-encoded imaging, respectively. In general, velocity-encoded imaging allows flow measurement in any vessel of the heart by multiplying the cross-sectional area of the vessel by the spatial mean velocity of blood flow. Like 2D-TTE, studies have shown that it is feasible to calculate a variety of hemodynamic parameters using CMR such as mean PA pressure, PVR, cardiac output, and PA acceleration time.82-84

One of the unique features of CMR is that, unlike 2D-TTE, it is possible to visualize the main PA and its branches. This allows one to measure parameters such as PA distensibility, which correlates strongly with severity of disease in PAH patients.85,86 In addition, 4D flow imaging by CMR measures all 3 directional components of the velocities of blood flow relative to time course of the cardiac cycle.87 This allows visualization of altered patterns of flow in the PA, and might be useful in providing greater mechanistic insight into consequences of pulmonary vascular remodeling (Figure 4). Using 4D flow of PA, wall shear stress was found to be significantly decreased in PAH patients compared to controls.88 In addition, vortices of blood flow are common in the main PA in patients with PAH, and the vortex duration appears to correlate significantly with mean PA pressure.89,90

**CONCLUSION**

The technologic and evidence base for both echocardiography and CMR in imaging the RV in PAH have clearly evolved dramatically in the last decade, but ultimately how have these advances impacted the question of which is the optimal RV imaging modality? While proponents of each modality may continue to fuel debate over which may be more effective in imaging the RV, in reality a general consensus is that these
imaging modalities are in fact complementary, each providing potentially unique information.

2D-TTE will remain the clinical workhorse of RV evaluation in PAH because it provides simple, reproducible, and meaningful single-plane surrogates of RV function. Newer echocardiographic techniques such as RV strain, 3D-TTE, and Ventripoint are promising in providing measurements of RV function, RV volumes, and RVEF without the limitations of CMR, but further technological improvements are necessary before these techniques can be incorporated into standard clinical practice.

Until then, CMR will remain the gold standard for measuring RV size and function. Beyond that, CMR can provide additional information on RV tissue characterization, perfusion imaging, and 4D flow imaging of the PA. Further research is needed to determine the clinical utility of these novel MRI measurements. RV imaging for PAH is rapidly evolving. Understanding what echocardiography and MRI currently have to offer is essential for the comprehensive evaluation and management of this patient population.

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Prognostication in Pulmonary Arterial Hypertension and Use of Current Risk Prediction Models

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Significant therapeutic advances in the field of pulmonary arterial hypertension (PAH), increased awareness and diagnosis, and changing patient demographics in the contemporary era have facilitated the development of better prognostic tools for predicting survival. However, overall patient outcomes remain poor, and measurement of most prognostic factors still occurs at the time of initial PAH diagnosis or enrollment into clinical trials. Treatment of PAH patients requires an individualized approach based on disease severity and burden of risk factors to improve patient outcomes. This article will focus on the use of risk prediction models to map and target individual disease trajectories to avoid future morbidity and mortality events.

Since the time of the National Institutes of Health (NIH) registry conducted in the 1980s of incident pulmonary arterial hypertension (PAH) cases reporting a median survival of 2.8 years after diagnosis,1 significant therapeutic advances in the field, increased awareness and diagnosis, and changing demographics of PAH patients in the contemporary era have facilitated the development of better prognostic tools for predicting survival. One-year survival in the NIH registry before modern therapies existed was a sobering 67%, compared to the 93% 1-year survival estimate of incident PAH cases from US REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management) from 2006–2009 (Figure 1).2 The French PAH registry, which enrolled patients over a 1-year period from 2002–2003, estimated a 1- and 3-year survival of 82.9% and 58.2% respectively.3 The NIH registry is no longer relevant for contemporary discussion in the current era, but it serves as an important reference for the natural history of untreated PAH patients. Despite superior survival compared with the NIH registry, overall patient outcomes remain poor, and measurement of most prognostic factors still occurs at the time of initial PAH diagnosis or enrollment into clinical trials, when referral and treatment delays may have substantially affected disease progression.4 We now appreciate that treatment of PAH patients requires an individualized approach based on disease severity and burden of risk factors to improve patient outcomes.5 Clinical experts are increasingly utilizing risk prediction models for prognosticating pulmonary hypertension (PH) groups and the individual patient both at time of diagnosis and in a serial fashion. With serial risk prediction, individual disease trajectories could be mapped and targeted with timely treatment interventions to avoid future morbidity and mortality events. Additionally, the field now desires to prioritize treatment goals associated with long-term outcomes rather than rely on short-term functional changes (ie, 6-minute walk distance or 6MWD) that may not meaningfully translate into improved survival.

PROGNOSIS ACCORDING TO AGE, SEX, AND ETIOLOGY

It is clear from contemporary registry data that the phenotype of patients diagnosed with PAH over the last few decades has changed. While the mean age of patients with idiopathic PAH (IPAH) in the NIH registry was 36 ± 15 years,1 we now recognize a shift in conjunction with an aging US population, where larger numbers of elderly patients are being diagnosed with PAH—at a mean age of 50 ± 14 years by current registry data (in REVEAL and the French registry). Older patients bring with them more advanced stages of the disease, lower age-related exercise capacity, and multiple comorbidities that impact outcomes, treatment decisions, and consideration for advanced therapies, as well as tolerability to aggressive pharmacotherapy. Not surprisingly, older patients have worse survival compared with younger patients despite the overall improved survival rates in the modern registries.

Female predominance for this disease is widely accepted and appears to have increased over time. Female patients now comprise up to 70% to 80% of registry participants with a 4.1:1 female/male ratio in REVEAL, compared with 63% of women and a 1.7:1 female/male ratio in the NIH registry.6 The majority of patients with IPAH and connective-tissue disease-associated PAH in REVEAL are women (80% and 90%, respectively). Female sex has been associated with a survival advantage compared to men and likely accounts for some of the striking gender predominance in prevalent cases. The overwhelming disease burden yet survival benefit conferred upon women requires further mechanistic study, but may be partly explained by the role of sex hormones in the pathogenesis of PAH and by beneficial right ventricular (RV) adaption and sex differences in treatment response.7

In contrast to age and sex, etiologies of PAH and prognosis therein affected has not appreciably changed. The same relative proportions of etiologies have been reported in the REVEAL registry.

Key Words—biomarkers, patient outcomes, pulmonary arterial hypertension, REVEAL registry, risk

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37
from 2006-2009 as were reported in the earlier US Pulmonary Hypertension Connection (PHC) registry from 1982-2006. Prognosis for patients with scleroderma-associated PH unfortunately remains inferior compared to other PAH subgroups, with 30% 1-year mortality in scleroderma PH vs 15% in IPAH.\(^9\)

Recent data indicate that contemporary survival in scleroderma PH patients has improved compared with historical controls, and early detection screening programs prior to symptom onset results in significantly better outcomes for these patients.\(^9\)

Human immunodeficiency virus (HIV)-associated PAH and IPAH share similar histopathological characteristics and survival despite a younger age at diagnosis in the HIV subgroup.\(^10\) The prevalence of HIV-PH is estimated at 0.5% and does not appear to have changed over recent decades.\(^11\) Prior to highly active antiretroviral therapy and PH-specific drugs, HIV-PH patients had an extremely poor outcome, with 1-year mortality of 50%. Current survival rates for patients with HIV-PH has improved to 88% at 1 year, and up to 20% of patients experience sustained normalization in hemodynamics with PAH treatment.\(^12\) PAH associated with congenital heart disease (CHD) will likely increase in prevalence, due to the increasing numbers of children with complex and/or repaired CHD who are surviving to adulthood. Despite the negative impact of concomitant PAH in CHD, the natural history of such patients remains favorable and is likely accounted for by their relative youth and better RV adaptation.

**Prognosis According to Hemodynamics, 6MWD, and Biomarkers**

As RV function is the key determinant of prognosis and a focal point of PAH treatment, hemodynamic parameters correlating with RV function and reserve, namely right atrial pressure (RAP), cardiac index (CI), and mixed venous oxygen saturation (SVO\(_2\)) are regarded as important independent prognostic factors in numerous studies. Current guidelines advise normalization of hemodynamics supporting greater RV stabilization rather than reversing the vascular disease process (ie, mean pulmonary artery pressure [mPAP] or pulmonary vascular resistance [PVR]). For instance, van de Veerdonk et al demonstrated that even when PAH therapies result in PVR reduction, patients may experience deterioration in RV ejection fraction (EF). Progressive RV dysfunction, irrespective of PVR change, assumes a more powerful role in prognostication than hemodynamics per se.\(^13\)

The historical use of 6MWD as a primary endpoint for treatment efficacy and as a survival surrogate has long been accepted, although several questions remain about its validity and prognostic assumptions. Some believe that 6MWD with its many limitations lacks the sensitivity and clinical significance to detect changes in right heart function. The 6MWD has largely lacked predictive power because many of the individual clinical studies were not designed to evaluate mortality and survival.\(^14\) It is furthermore uncertain whether absolute responder thresholds of 6MWD suggested as >380 m from Sitbon et al or >400 m associated with improved survival in REVEAL are as useful as relative improvements in 6MWD.\(^15,16\)

A recent meta-analysis evaluating the results of 22 clinical trials concluded that favorable treatment effects linked to lower all-cause mortality, PAH hospitalization, transplant, and need for rescue therapy were not predicted by changes in 6MWD alone.\(^17\) Improvement in the 6MWD of ≥41.8 m was evidently found to be the minimally important difference that correlated with lowered odds of a clinical event at 12 weeks, but this again accounted for only 22% of the treatment effect.\(^18\) Thus, it seems that change in 6MWD is at best a modestly valid surrogate for clinical events. Additionally, clinical studies and clinicians heavily emphasize improvements in 6MWD to determine clinical response to treatment, but until recently have extracted less insight on the meaning of a deteriorating walk distance. Farber et al recently showed that worsening 6MWD, but not a stable or improving 6MWD, was strongly associated with survival and that a 15% reduction in 6MWD may be necessary for this observed effect.\(^14\)

Despite the challenges of identifying novel noninvasive markers of disease, the study of biomarkers for diagnosis, pathogenesis, disease progression, and treatment guidance in PAH and RV dysfunction remains an active area of investigation. The many different pathobiological mechanisms involved in PAH have led to an explosion of disease-specific biomarkers (Table 1), but to date, none of these has demonstrated all the characteristics of the ideal biomarker.\(^19\) Evidence suggests that a multiple biomarker approach may yield incrementally more information on disease state and prognosis rather than reliance on a single marker.

Of all the markers, brain natriuretic peptide (BNP) and its cleavage product, N-terminal prohormone BNP (NT-proBNP), are the most widely studied and clinically relevant markers for outcome prediction in current practice. B-type natriuretic peptide is elevated in a number of PH subtypes and correlates with acute and chronic hemodynamic derangements indicative of RV stress and...
therapy responsiveness. It also acts as an independent predictor of mortality in PAH (eg, lower survival observed in patients with baseline BNP \( \geq 150 \text{ pg/mL} \)).\textsuperscript{20} The BNP level is the only biomarker currently included as a potential treatment goal in PAH (Table 2). Rather than trying to achieve a “normal” BNP as current guidelines suggest, it may be more practical to individualize BNP values, taking into account the influence of age, sex, and renal function when trying to attain an individual’s lowest possible BNP or NT-proBNP with titratable therapies. It remains to be seen whether natriuretic peptide-guided pharmacologic therapy can significantly reduce morbidity and mortality related to right-sided heart failure in PAH, as shown in patients with chronic left heart failure, and how this ranks compared to simultaneously important hemodynamic and imaging markers of RV function.

The proliferating data from ongoing biomarker studies must therefore be critically interpreted before biomarkers can affect current management in PAH.

### Treatment Goals and Clinical Response Using Multiple Risk Predictors

No single risk parameter can satisfy the need for reliable long-term prognostication. Furthermore, we lack agreement on which parameter(s) carry the greatest weight and validity for directing therapy. Composite treatment goals are more meaningful and a strategy aimed at integrating hemodynamic, clinical, and RV imaging metrics; biomarker data; and treatment goals holds greater promise for outcome prediction. It is becoming clear that defining multiple goals of interest with absolute and relative thresholds or specific cut points to target with pharmacotherapy is crucial. It is also apparent that follow-up risk assessment is as, if not more, important than baseline evaluation. In a study of PAH patients by Nickel et al, those who attained World Health Organization (WHO) functional class (FC) I/II status, CI >2.5 L/min/m\(^2\), SVO\(_2\) ≥65%, and NT-proBNP <1800 pg/mL after targeted therapy did better than those who did not, irrespective of baseline risk status.\textsuperscript{21} An integrative and individualized approach using multitiered parameters reflecting one’s clinical response over time is likely to be more informative for outcome prediction and disease management.

### Table 1. Different pathophysiologic mechanisms and associated biomarkers

<table>
<thead>
<tr>
<th>Pathobiology</th>
<th>Biomarker</th>
<th>Availability</th>
<th>Specificity</th>
<th>Prognostic Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurohormonal Activation</td>
<td>● Natriuretic peptides*</td>
<td>+++</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>● Endothelin-1</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>● Adrenomedullin</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>● Copeptin</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>End organ failure</td>
<td>● Creatinine</td>
<td>+++</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>● Sodium</td>
<td>+++</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>● Uric acid</td>
<td>+++</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Myocardial injury</td>
<td>● Troponin</td>
<td>+++</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Inflammatory markers</td>
<td>● Interleukins</td>
<td>+++</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>● C-reactive protein</td>
<td>+++</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Vascular remodeling</td>
<td>● Von Willebrand factor</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>● Angiopoietin</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>● Growth differentiation factor</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Genomics/Proteomics</td>
<td>● Unknown</td>
<td>–</td>
<td>+++</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*Only biomarker to date used in clinical practice and included in PH therapy-driven guidelines.

### Table 2. Variables Used in Clinical Practice to Determine Response to Therapy and Prognosis in PAH Patients

<table>
<thead>
<tr>
<th>Functional Class I or II</th>
<th>Echocardiography/CMR Normal/near-normal RV size and function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodynamics</td>
<td>Normalization of RV function using RAP &lt;8 mm Hg and CI &gt;2.5-3.0 L/min/m(^2)</td>
</tr>
<tr>
<td>6MWD &gt;380 to 440 m</td>
<td>Cardiopulmonary exercise testing Peak VO(_2) &gt;15 mL/min/kg and EqCO(_2) &lt;45 L/min</td>
</tr>
<tr>
<td>B-type natriuretic peptide level</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Adapted from McLaughlin VV et al.\textsuperscript{22} CMR = cardiac magnetic resonance; RV = right ventricular; RAP = right atrial pressure; CI = cardiac index; 6MWD = 6-minute walk distance; VO\(_2\) = peak oxygen consumption; EqCO\(_2\) = ventilator equivalent for carbon dioxide.
Current treatment guidelines recommend assessing multiple parameters for gauging the efficacy of a therapy. Updated treatment goals for PAH include: New York Heart Association FC I or II, 6MWD ≥380 to 440 m, cardiopulmonary exercise testing with peak oxygen consumption (VO₂) >15 mL/min/kg and ventilator equivalent for carbon dioxide <45 L/min, BNP levels approaching “normal,” echocardiography or cardiac magnetic resonance imaging (CMR) revealing near-normal RV size and function, and RAP <8 mm Hg and CI >2.5 to 3.0 L/min/m², derived from previously published prognostic levels in PAH patients and the priority given to stabilizing RV function (Table 1). More recently, riociguat-treated patients with PAH and with inoperable or persistent chronic thromboembolic pulmonary hypertension (CTEPH) in the PATENT-1 and CHEST-1 studies, respectively, were assessed against placebo controls for “positive response” to therapy, defined as ability to meet prespecified criteria. In both studies, a positive responder threshold was defined as an increase in 6MWD ≥40 m, 6MWD ≥380 m, CI ≥2.5 L/min/m², WHO FC I/II, NT-proBNP <1800 pg/mL, and RAP <8 mm Hg. In the CHEST-1 study, an additional criterion of achieving PVR <500 dyn·sec·cm⁻⁵ was included because of its common use in CTEPH patients for prognostication. These studies assessed both individual responder endpoints and the combined responder endpoint, and concluded that riociguat increased the proportion of patients achieving this combined endpoint compared with a placebo group. In PATENT-1, treatment with riociguat after 12 weeks increased combined endpoint responsiveness from 15% at baseline to 34% of patients, but was largely unchanged in the placebo group. In CHEST-1, the proportion of patients meeting combined responder criteria increased from 5% to 25% after 16 weeks of treatment with riociguat, but again remained unchanged in the placebo arm. The odds ratio for achieving a combined responder endpoint with riociguat compared to placebo was 4.98 (95% CI 1.68–14.77, P=0.0007). Although the proportion of patients achieving a combined endpoint was lower than the proportion achieving individual criteria in both of these studies, these analyses lend further support to using composite treatment goals over a range of individual responder variables for survival prediction.

REGISTRIES AND RISK SCORES
Modern-day registries have tremendously expanded our knowledge on the demographics, clinical and hemodynamic profiles of patients, and epidemiology and survival of contemporary PAH cohorts. From registry data, collective determinants of survival on multivariable analysis can be identified and used to create prognostic equations to predict survival at any point in a patient’s disease course. The NIH registry was the first registry to evaluate survival and develop a prognostic model of untreated patients in 1981. Since that landmark study, 4 recent registries (French registry, PH registry, Mayo Clinic registry, and—the largest of all—REVEAL registry) have introduced better discriminatory models that have shown improved survival with available PAH therapies. Each of these registries draw from varying numbers of patients, including both prevalent and incident cohorts, different observation periods, diverse PAH subgroups, and periods of survival, yet the key predictors of outcome are surprisingly congruent across the studies. These include sex, FC, exercise capacity by 6MWD, and RAP and cardiac output (CO) as invariably powerful hemodynamic parameters in PAH. In fact, hemodynamic parameters were some of the first used for predicting outcome from the NIH registry, which derived its survival equation using RAP, CI, and mPAP as predetermined variables that were each independently predictive of death. Although risk models have limitations and require broader validation in different patient populations, the models offer a stronger framework for risk prediction than using single predictors of the disease.

Despite improved observed survival rates in modern-day PAH registries, it is important to acknowledge that survival in almost all registries, including REVEAL and the French registry, examined newly diagnosed and prevalent cases—the latter of which can introduce a survivor bias. Thus, generalizing results from registry data must take into account the population studied, time from symptom onset to diagnosis, biases in treatment access, and understanding of which patients the results can be applied to. For instance, survival estimates from the time of enrollment in a predominantly prevalent cohort can be misleading if then used to predict outcomes in newly diagnosed patients.

Furthermore, clinicians must understand the registry population, different inclusion and exclusion criteria, and epidemiology of PAH patients being studied to derive survival estimates, and whether applicable to the intended population or patient for whom risk prediction is desired.

Despite being derived in a combined prevalent and incident cohort at time of enrollment, the REVEAL PAH risk score equation maintained its predictive power and was validated in a separate cohort of newly diagnosed patients. The REVEAL equation was also externally validated in matched patients from the French registry, as well as in other distinct PH populations, and shown to have good discriminatory power to predict 1-year and 5-year survival.

More recently, the REVEAL model performed well for risk prediction in non-PAH patients, suggesting its potential for broader application in a more general PH population. Recognizing that a vast majority of patients have non-PAH or multifactorial PH, future registry analyses should be directed at broadening to other PH groups, namely Group 2 and Group 3 PH. The advantage of doing so is to better understand the clinical course and how to approach this large, heterogeneous, at-risk population who presently do not qualify for traditional PH treatments.

The predictors of 1-year survival from patients enrolled in REVEAL were evaluated in a multivariate analysis to create a weighted risk formula to be used at any time in the disease course. The final
prognostic equation contains 19 predictive factors, each of which are independently predictive, and the equation has excellent discriminatory power (c-index 0.772) for distinguishing between patients who are likely to die vs those likely to survive.\textsuperscript{30} Given a pair of randomly selected patients, one who dies and one who survives, the c-index is an estimate of the probability that the patient who died had a higher predicted chance of death (the closer the c-index is to 1.0, the better the model discriminates). The REVEAL equation has greater discriminatory ability in contrast, for instance, to the NIH equation, which incorporated 3 hemodynamic variables a priori (c-index 0.588), and to the French registry, which yielded 3 variables as well (sex, CO, 6MWD) on multivariable analysis significantly associated with survival (c-index 0.57). No c-index was calculated for the PHC equation. It is possible that REVEAL’s superior discriminatory ability is due to an inclusion of multiple covariates, which was preserved even when patients lacked or were missing some of the predictive factors in the equation (the average patient in REVEAL had data only for 16 of the 19 factors).

In contrast to the French registry equation, which is not intended to predict individual patient outcomes but rather is used for survival comparison in other PAH cohorts, the REVEAL equation has been transformed and validated into a risk calculator that provides a numerical value for the risk score that can be used clinically for the individual patient at diagnosis and in serial follow-up (Figure 2). Five risk strata based on risk scores have been developed and are shown in Figure 3. REVEAL can even be used when missing variables, without sacrificing the significant predictive power of the equation as shown by Cogswell et al.\textsuperscript{31} This analysis selectively removed the right heart catheterization and pulmonary function testing data, specifically a PVR $\leq$32 Wood units or diffusion lung capacity for carbon monoxide $\geq$32%, which represent extremes not met in a majority of patients, and may explain why this model performed nearly identically to the full original REVEAL model (c-index 0.759 compared with full REVEAL 0.765, $P=0.92$). The analysis also modified the full REVEAL model to include only noninvasive variables of the PAH WHO diagnostic group, WHO FC, BNP, renal function, and RAP by echocardiogram and found comparable 1-year survival discrimination with the full model. The preservation of this model perhaps suggests these are the most salient predictors and best suited for long-term disease monitoring. This further highlights that a more simplified use of the REVEAL score may be appropriate, clinically advantageous with broader applicability, and accurate even when clinicians lack some of the variables at diagnosis and follow-up.

Because all variable data are rarely captured at a single point in time due to the reality of clinical practice, the calculator allows for entry any time a new variable becomes available or is reassessed. One major limitation of this, however, is that a patient’s measured health state using the risk calculator at disparate points in time may not accurately signal the current disease state.
hypertension. The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial
vascular disease through regular risk modeling. In this manner, REVEAL and future risk models may enhance the individualized patient approach and actively inform treatment goals and guide timing of interventions.

FUTURE DIRECTIONS USING PROGNOSTIC TOOLS

Presently, risk scores are not utilized as endpoints for clinical trials, and there is more to be done to characterize the prognostic effects of treatment in an aggregate model. For instance, it is understood that a patient initiated on intravenous prostacyclin has a disease trajectory different from one not yet on prostacyclin, despite the 2 possibly having identical REVEAL risk scores for different reasons. Before risk scores can be utilized for clinical response outcomes or encouraging a goal-oriented therapy approach, we have to first interpret treatment effect on risk scores for the study period or over a patient’s lifetime. If we use the Seattle Heart Failure Model as an example of individual risk prediction in a broad heart failure population, this model permits mortality projections to change based on addition or withdrawal of evidence-based therapies, and can predict mode of death such as pump failure or sudden cardiac death. It is important to recognize that unlike heart failure, the field of PAH lacks robust evidence-based data for a majority of therapies, thus explaining the challenge of integrating drug interventions in current models. For instance, we do not fully know the relative risks of single vs combination therapy vs parenteral therapy, and whether particular drug selection affects survival or is simply a signal for disease severity. Until we better understand the relative risks or benefits of the available therapies, it will be challenging to derive models that change according to a chosen drug strategy.

In the future, we should elect to design risk models that enable selection of therapies while considering patient preference, include advanced options and
newer device-based therapies, provide realistic projections for the individual patient and family, and more precisely define those factors that are important for disease management. In the last 10 years, the focus on improvement and/or preservation of RV function has increased. The study of RV pathology in PAH has become more sophisticated to potentially allow inclusion of novel RV specific factors (ie, RV strain, RV-PA coupling, RV responsiveness to stress or exercise) in future models. An “RV-centric” strategy may be the essential link for stronger modeling and disease prediction. Identification of newer disease-modifying targets and study of broader phenotypes will be necessary to improve existing tools and positively affect the care of PH patients.

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What Is the Utility of Evaluating Patients for Exercise-Induced Pulmonary Hypertension?

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**EXERCISE-INDUCED PULMONARY HYPERTENSION**

Pulmonary hypertension (PH) is currently defined by a resting mean pulmonary artery pressure (mPAP) that is ≥25 mm Hg. Prior to 2009, the definition of PH also included those with mPAP ≥30 mm Hg with exercise, while the diagnosis of exercise-induced PH was made by observing a normal resting mPAP that increased to >30 mm Hg with exercise. Kovacs et al, however, demonstrated in 2009 that exercise-induced increases in mPAP occurred naturally with age. In their pooled analysis of 1187 healthy individuals from 47 different studies, patients over the age of 50 years had an average mPAP with exercise near 30 mm Hg. These data, coupled with uncertainty regarding the proper type, posture, or intensity of exercise necessary for diagnosis, led to the removal of exercise-related definitions from the PH guidelines in 2009.

Nonetheless, exercise-related changes in mPAP may have potential utility. This update will focus on recent studies illuminating pitfalls in the performance and interpretation of exercise hemodynamics and the current data supporting their clinical and diagnostic potential.

**DETERMINANTS OF mPAP AND ITS NORMAL RESPONSE TO EXERCISE**

Before defining a pathologic increase in mPAP, it is important to review the factors that determine mPAP, as well as the normal response of mPAP to exercise. mPAP is a function of the product of pulmonary vascular resistance (PVR) and cardiac output (CO), as well as downstream left heart pressure (estimated by pulmonary artery wedge pressure (PAWP)):

\[
mPAP = (PVR \times CO) + PAWP
\]

Pressure must always be considered in the context of flow, or CO, since mPAP will rise with increases in CO. In the normal exercising individual, an increase in CO is accompanied by a fall in PVR. This is due to a combination of pulmonary vascular recruitment and distension of the pulmonary resistance vessels. With significant pulmonary vascular pathology, however, PVR may only minimally decrease or even increase, leading to a rise in mPAP.

By examining pressure-flow relationships from available data in healthy individuals, Naeije, Lewis, and colleagues proposed that the slope of the mPAP/CO relationship should be no greater than 3 mm Hg/(L/min). Although there is some curvilinearity to the mPAP-CO relationship, it can generally be approximated as linear, especially when measures are taken at multiple time points during exercise.

Notably, while the mPAP/CO slope is useful to define abnormal vs normal responses, it cannot differentiate if a rise in mPAP is due to a failure of PVR to fall or a rising PAWP from left heart disease. In addition, the PAWP must be carefully measured during exercise, since an abnormal escalation in PAWP may lead to exercise-induced increases in mPAP, as PAWP rises normally in response to exercise. Indeed, studies of healthy individuals have shed light on the normal physiologic response by demonstrating that exercise can lead to increases in PAWP of 10 mm Hg or more in some cases. Upright exercise leads to PAWP values that are approximately 5 mm Hg less, on average, than those seen with supine exercise, although the absolute change in PAWP is similar. Based on these findings, we...
consider an abnormal PAWP to be $\geq 25$ mm Hg with supine exercise or $\geq 20$ mm Hg with upright exercise. Because right atrial pressure (RAP) approximates pericardial pressure in most situations, examining the transmural left ventricular (LV) filling pressure (PAWP – RAP) may also be useful to tease out the component of PAWP elevation that is related to LV pathology rather than pericardial constraint.10

MEASURING EXERCISE HEMODYNAMICS

There are several important considerations to ensure proper data collection when performing exercise hemodynamic measurements. First, care must be taken to ensure proper transducer leveling, especially if upright exercise is used. Bicycle exercise is preferred to upper extremity exercise to avoid unwanted increases in systemic vascular resistance. Of course, indirect or modified Fick cardiac output estimations (which assume fixed oxygen consumption) cannot be used during exercise, as oxygen consumption increases during exertion. Although there are few data comparing thermodilution cardiac output (TD CO) to direct Fick measurements (direct measures of oxygen consumption) during exercise,11,12 the latter is generally preferable and has been used in most studies examining exercise hemodynamics.8,9,13-15 Furthermore, unless a high-fidelity catheter is being used, mPAP, rather than pulmonary artery systolic and diastolic pressures, should be reported due to excessive catheter ringing and motion artifact that is usually present during exercise measurements.16

Because exercise can lead to dramatic swings in intrathoracic pressure, measuring end-expiratory pressures may overestimate true pressure, especially in the setting of lung disease. Boerrigter et al recently showed that averaging pressures over the full respiratory cycle during exercise more closely approximated true pressures (confirmed by direct esophageal pressure measurements) in patients with severe obstructive lung disease.13 Although we do not yet have similar studies in patients without lung disease, averaging values over the entire respiratory cycle is considered the preferred method.16

THE USE OF EXERCISE-INDUCED INCREASES IN MPAP AND PAWP

When reliably and accurately measured, we believe exercise-induced changes in mPAP and PAWP may be useful in at least 4 clinical scenarios: (1) differentiating Group 1 PH from Group 2 PH, (2) identifying occult but symptomatic left heart disease, (3) identifying symptomatic exercise-induced pulmonary arterial hypertension (PAH), and (4) assessing right ventricular (RV) contractile reserve (Table 1).

Identifying Occult But Symptomatic Left Heart Disease

In 2010, Borlaug and colleagues found exercise measurements to be helpful in the diagnosis of occult left heart disease, or what they termed “early HFpEF.”14 In these patients, it is thought that worsening diastolic reserve leads to symptoms and hemodynamic changes with exertion but not at rest. The group retrospectively reviewed hemodynamic data of patients being evaluated for unexplained dyspnea who had normal LV ejection fraction ($\geq 50$%), normal resting hemodynamics, normal B-natriuretic peptide levels, and no obvious left heart or pulmonary disease. Supine exercise PAWP $\geq 25$ mm Hg was used to differentiate “early HFpEF” patients from those with noncardiac dyspnea. Exercised-induced increases in pulmonary artery systolic pressure (PASP) $\geq 45$ mm Hg also correlated well with exercise PAWP and predicted early HFpEF with 96% sensitivity and 95% specificity. These patients also demonstrated impaired heart rate, cardiac index, and systemic vascular resistance responses characteristic of more advanced HFpEF patients.14

Identifying Exercise-Induced PAH

As described above, exercise-induced PAH previously referred to the patient with normal mPAP at rest but $\geq 30$ mm Hg with exercise. While some believed this to

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Table 1. Potential Clinical Scenarios for the Use of Exercise-Induced Hemodynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Differentiating Group 1 and 2 PH</td>
<td>PAH = pulmonary hypertension; HFpEF = heart failure with preserved ejection fraction; PAWP = pulmonary arterial hypertension; RV = right ventricle</td>
</tr>
<tr>
<td>2. Identifying Occult Left Heart Disease, or “Early HFpEF”</td>
<td></td>
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<tr>
<td>3. Identifying Exercise-Induced PAH</td>
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<td>4. Assessing RV Contractile Reserve</td>
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When resting hemodynamic investigations lead to clinical equipoise between Group 1 PH and HFpEF-PH, clinical characteristics and echocardiographic parameters may be useful to assist in diagnosis.18 When still unclear, hemodynamic assessment with exercise to elicit pathologic increases in PAWP can help support the diagnosis of HFpEF-PH.1,19 While saline boluses have also been used to diagnose occult HFpEF, it was recently suggested that exercise may lead to more dramatic increases in PAWP compared to saline, and therefore be more sensitive for the detection of HFpEF.9,19 That said, an important caveat of this study was that exercise pressures were measured at end-expiration.
be an early phase of PAH, others considered this a stable variant. In favor of the former hypothesis, exercise-induced increases in mPAP >30 mm Hg have been shown to be associated with dyspnea and fatigue symptoms. It has also been shown that some patients with PAH demonstrate exercise-induced elevations in mPAP that precede resting elevations in mPAP.

Tolle and colleagues sought to characterize this group of patients in 2008 by retrospectively reviewing 3 years of invasive hemodynamic exercise data in patients with exertional dyspnea. They found that patients with exercise-induced increases in mPAP >30 mm Hg (PAWP <20 mm Hg) exhibited a hemodynamic profile that was intermediate between those of normal patients and resting PAH patients (in terms of maximal oxygen consumption [VO2max; % predicted], COmax[% predicted], RV ejection fraction, alveolar-arterial difference, and PVR). Examining the relationship between exercise mPAP and VO2 revealed 2 distinct patterns: 1) a “takeoff” pattern where mPAP rose most significantly during late exercise, possibly related to vasoconstriction; and 2) a “plateau pattern” where mPAP failed to rise with increasing VO2, possibly indicative of RV dysfunction or worsening tricuspid regurgitation. The takeoff pattern was seen in most normal patients, whereas the plateau was more commonly seen in those with PAH. Not surprisingly, the plateau pattern was associated with reduced maximum exercise work, peak VO2, and CO. Longitudinal data were not available in this study, nor was information on the more recently proposed mPAP/CO slope.

Identification of exercise-induced PAH may categorize a group of patients responsive to early treatment. A small, single-centered, prospective pilot study was performed using the endothelin-antagonist ambrisentan (Letairis, Gilead Sciences) to treat exercise-induced PAH associated with systemic sclerosis (SSc). In the 11 patients that completed the 24-week study, there were significant improvements in mean PVR with exercise, 6-minute walk distance, exercise CO, mPAP, and total pulmonary resistance. Bosentan (Tracleer, Actelion Pharmaceuticals) was also studied in 2 pilot studies—one of 10 patients and one case report of a single patient—and was found to improve hemodynamic parameters in patients with SSc-associated exercise-induced PAH.

It should be noted that therapeutic studies using the newly proposed definition of exercise-induced PAH (mPAP/CO slope >3 mm Hg/L/min) in the setting of a normal PAWP response have not been performed. Until such studies are performed and more supporting data are available, treating exercise-induced PAH would be premature.

### Assessing RV Contractile Reserve

Exercise-induced changes in mPAP and RV function (RV contractile reserve) may be useful to predict prognosis in PH as well as identify patients with “hidden” RV failure. Blumberg et al found that in patients with PAH or inoperable chronic thromboembolic pulmonary hypertension (CTEPH), peak cardiac index attained with exercise correlated with peak VO2 and, along with the mPAP/CO slope, was one of the only hemodynamic variables that predicted mortality. In another provocative study, 124 patients with confirmed PAH or inoperable CTEPH underwent exercise-stress Doppler echocardiography and cardiopulmonary testing, and were then prospectively followed for a mean of 3.0 years. Along with peak VO2, an inability to augment PASP during exercise (increase <30 mm Hg) predicted worse survival when compared to a more robust increase in PASP (>30 mm Hg) with exercise.

Identifying a patient with “hidden” or subclinical right heart failure could have important implications for early PH treatment strategies as well as for LV assist device implantation in heart failure patients. Measuring coupling between RV contractility and pulmonary arterial (PA) load is the gold standard for assessment of RV function and may detect abnormalities even when other clinical measures are normal. RV-PA coupling, however, is difficult to measure clinically. In an animal model of PAH, RV reserve closely correlated with resting RV-RA coupling, suggesting that RV reserve may be a useful surrogate.

Several studies have looked at RV reserve in PH patients. Recently, Claessen et al found that patients with CTEPH after pulmonary endarterectomy demonstrated a reduced peak CO, reduced VO2, and elevated mPAP/CO slope with exercise, despite having normal resting parameters. This impaired RV reserve was also seen by Bonderman and colleagues in a study of CTEPH patients with persistent exercise limitation after endarterectomy. While these studies focused on CTEPH, the use of exercise evaluation to determine RV contractile reserve will likely play an important role in many categories of PH.

### CONCLUSION

Although removed from the formal definition of PH in 2009, exercise-induced changes in mPAP and PAWP do occur and can be useful if properly performed. Although we believe additional work is needed before exercise-induced PAH is reintroduced to the guidelines, there are several clinical scenarios in which assessing exercise hemodynamics may be helpful. These include differentiating between Group 1 and 2 PH, identifying occult or early stage HFpEF, identifying exercise-induced PAH, and assessing RV contractile reserve and prognosis in patients with known PH.

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**Prognostic Indicators for Pulmonary Hypertension**

*Advances in Pulmonary Hypertension* editor-in-chief Charles Burger, MD, Professor of Medicine at Mayo Clinic College of Medicine and Medical Director, PH Clinic, Mayo Clinic, Jacksonville, Florida, convened this issue’s guest editors Ioana Preston, MD, Co-director, Pulmonary Hypertension Center, Tufts Medical Center, Boston, and Raymond Benza, MD, Program Director, Heart Failure, Transplant, Mechanical Circulatory Devices and Pulmonary Hypertension, Western Pennsylvania Allegheny Health System, and Professor of Medicine, Temple University, Pittsburgh, along with editorial board member Jonathan Rich, MD, Assistant Professor of Medicine, Northwestern University Feinberg School of Medicine, Medical Director, Mechanical Circulatory Support Program, Bluhm Cardiovascular Institute, Northwestern Memorial Hospital, Chicago, for a wide-ranging discussion about clinicians’ ability to prognosticate about patients’ disease.

**Dr Burger:** The articles that are in this issue range from biomarkers to right ventricular imaging to risk scoring. That is quite a breadth of topics. It allows this particular discussion to touch on some of the gaps in those areas and, of course, provide expert opinion regarding where we are as of 2015 with our ability to prognosticate with PAH. I’ll start the discussion by throwing out a question to the panel, beyond the obvious utility, the ability to prognosticate with our patients, what above and beyond is so important about our ability to determine prognosis in a more refined way? Ioana, what do you think?

**Dr Preston:** It’s a very interesting question and complex, both question and probably answers. So Charlie, pulmonary hypertension is such a complex disorder. It involves malfunction not only of the pulmonary vasculature, but the right heart, also the left heart. And it ends up being a truly systemic disease that affects the entire body. So taking up very fine details of the severity of the disease is not easy. And that entails understanding not only the pathophysiology but also ultimately how long our patients will survive, how well will they survive, their quality of life. And how can we adapt our therapies that we have available to improve several aspects of their disease and their life.

**Dr Burger:** Do others have comments?

**Dr Benza:** Yeah, I have probably a few things that I try to keep in mind. And what I try to teach is the reason why risk prognostication should be done with some frequency in patients with this disease. And most importantly, it’s to diagnose the rapid progressors, particularly those who are newly diagnosed or have been recently discharged from the hospital. Because if you look at the attrition rates with pulmonary hypertension, these are the patients who will survive the least and the ones who you need to be on top of, in order to amplify their therapy, to improve their long-term outcomes. And I think identifying these rapid progressors is incredibly important in the community setting and among less experienced practitioners. And risk prognostication allows some equalization of the playing field in those less experienced settings, so that these appropriately ill patients can be identified and have their therapy changed accordingly. I think risk prognostication also provides a basis for the institution and timing of types of therapies, based on needs and risks, so the sickest patients get the IV prostacyclins and the least sick patients perhaps get the oral analogs. I think it provides an opportunity to enhance consistency among therapies, so that everyone who is class 4 gets an IV prostacyclin, such that these patients are treated more according to guideline therapies. And obviously also, risk prognostication is essential for the appropriate timing for lung transplantation, which we all know is really the only cure for this disease. Many of our colleagues who do lung transplantation fret when we send them patients who are too advanced in their illnesses, such that their life expectancy is disproportionally judged by at least in the U.S. by the LAS score. But I think risk prognostication for those four reasons is essential for our patients.

**Dr Burger:** Certainly, this issue contains a very well done review on biomarkers, serum biomarkers. What does the panel feel is the current state of affairs with serum biomarkers and how they should be used in the practice and their potential role in more complex scores, which we’ll get to as well, as we evaluate our patients?

**Dr Preston:** I think biomarkers are a very useful tool for any disease. Now, in pulmonary hypertension, although different groups have looked at several biomarkers to try to identify patients at risk for progression or patients who have severe disease, so far in clinical practice, we currently use brain natriuretic peptide or its precursor, anti-pro BNP. I think at least in my practice, it is a useful marker to pick up subtle changes in volume status, subtle changes in disease progression, maybe before it’s completely overt and clinically obvious. So that’s, I think, the main markers, serologic markers, that we can use currently.

**Dr Benza:** I think our issue with biomarkers in the current state of treatments is that the studies that have analyzed these biomarkers have been usually single center or several center studies and so their utility I think is limited in scope because of the small populations they’ve been studied in.
really, the only biomarkers that have been studied with any significant degree of patient population is that natriuretic peptides, as Ioana just mentioned. And here, they do hold fairly substantial weight and risk prognostication. But I think what the important thing to remember is that biomarkers in and of itself may be important, but they're much more important when they are utilized in the context of multiple other risk factors or prognosticators, so that you don’t hang your hat on just one thing and they're used more to paint the entire picture and to paint the entire picture.

Dr Preston: I agree.

Dr Burger: Before we get to putting various components together, I would ask if Jonathan might address something that Ioana alluded to. And that is, what exactly does a rising BNP mean? And so from a practical perspective when you’re seeing a patient in a clinical who has doubled their BNP, how do you sort through volume retention versus RV dysfunction?

Dr Rich: Well, I think that’s a great question about how to best utilize BNP levels in clinical practice. We know that the presence of an elevated BNP or NT-pro BNP is an ominous prognostic marker. And I also agree with one of the previous comments that BNP levels, when used in conjunction with other known prognostic factors in PAH, is ultimately going to be even more powerful. But your question is a really important one as it contributes to the conversation about how to know when to pull the trigger on more intensive therapies and leads us to ask some intriguing questions. For instance, are there ways to utilize biomarkers such that changes in BNP could be used to reliably predict response to therapies? A lot of this work is being done in the left heart failure arena. In PAH, can you rely on the finding of serial improvements in BNP to suggest that that particular patient is favorably responding and is likely to continue to respond to current therapy? Conversely, to your question Charlie, can you reliably consider a rising BNP as a marker that specifically the status of the RV is getting worse? Personally, if my patient had a doubling of his/her BNP level, this would worry me that it is a reflection of worsening RV wall stress and in PAH, it is all about the RV. But is that rise in BNP alone sufficient by itself to warrant a closer investigation into whether we need to start to make changes to therapies or perhaps as you indicated, may it in some instances simply be a reflection of a little extra fluid retention, a change in renal function, etc and not necessarily indicative of a marked change in RV function? So I think that the particular role of BNP, not just the actual elevation of BNP, but the changing and dynamic nature of BNP, can be leveraged in both prognosticating and clinical decision making, perhaps as part of a larger panel with other emerging biomarkers, whether it be high sensitivity troponin or some of the newer ones that are emerging, like ST2 and so forth. The utility of having a panel of markers to use is likely to be additive in value to BNP alone when trying to make clinical decisions. But for now, I will simply conclude that in both left and right heart failure, a rising BNP is something I don’t like to see. And an improving BNP, of course I’m happy with. But the ultimate question remains, can we utilize biomarkers in a more refined way to really guide both decision making and prognostication?

Dr Burger: Ray, obviously you’ve done tremendous work in working with the REVEAL registry database to develop the REVEAL risk score. And that’s discussed in this issue in the manuscript by Dr. Aggarwal as a validated methodology for prognostication. What would you advise the practitioners as to the role of calculating the score during outpatient visits for patients under treatment for PAH?

Dr Benza: Yeah, I think the REVEAL calculator, just like in any other individual markers that we’re talking about, are tools that you fill your tool belt with. It just happens to be one of the biggest hammers in your tool belt. And I don’t think the REVEAL calculator is meant to be used on every touch point with the patient. But certainly, with some degree of frequency throughout the course of a patient’s disease, the score can be used several times per year to make sure you’re on track with that patient. And I think the recent literature that we publish with the serial use of the score suggests that not only are changes in the score important in predicting outcome but use of the absolute score serially is equally as important. So both the delta change and the repeat absolute score seem to be very important. And we have capitalized on this and we’ve incorporated the calculator into our daily practice at our center. And I think it has resulted in a significant improvement, both in identifying patients that need more aggressive therapy and has improved our long-term outcome, at least within our own practice. So I advocate the regular use of it, again not every single time someone comes to clinic, but certainly they can give you an idea how people respond to many of the things that we do routinely on a clinical visit for a PAH patient are vital parts of the calculator, assessing their functional class, you know, assessing them for volume, doing their BNP levels, doing your 6 minute walk test. And so you can use the calculator roughly in those situations to guide you, but periodic use of the calculator throughout a patient’s course I think is very valuable in identifying people who are moving in the wrong direction and those who you can pull back by appropriately amplifying their therapeutics.

Dr Preston: So Ray, not all the parameters, the 19 parameters in the REVEAL score, are newly recorded within a visit. How do you take into account missing parameters?

Dr Benza: So in the construction and initial calibration of the calculator, we took into account that all tests weren’t going to be done at any particular interval. And the original algorithm accounts for missing-ness of data. And some of that is accounted in by the correction factor that you note that you have to use when you use the actual raw calculator. So it does account for missing
data. And remember, the calculator really only needs seven evaluable factors for it to really maintain good calibration, so you don’t need all the factors at all the time. The one factor that seemed to remain statistically important for long periods of time were the hemodynamics. So if someone had a very adverse right atrial pressure, the effect of that right atrial pressure seems to last for a period of time, even after it is improved upon with use of diuretics or other medications. The way we use it in our own practice is we use the calculator at least three times a year, so with changes in therapy, we will recalculate scores after a period of time where we think that the therapeutic has kicked in and equalized. And we certainly use it on a yearly basis when people come in for their yearly risk stratification. So patients at our center usually come in yearly for a risk stratification. Some of this – most of the time, this includes standardized right heart catheterizations. Other times, it doesn’t. But at least on a yearly basis, we use this to guide whether we have appropriately managed that patient over the course of the year. In the newly diagnosed or recently decompensated patients, we use the calculator probably a little bit more frequently than yearly. And we found that to be a useful way to utilize it.

Dr Burger: Ray, on a practical note, since the patients obviously, and to their credit, are very focused on their disease and sophisticated in their understanding of what we’re measuring, so they will ask about their 6 minute walk distance or their BNP. And as you would calculate this score, do you share the actual number with the patients or how do you handle the potential challenge of the patient perseverating, if you will, on their calculated score during their visit?

Dr Benza: Well, I think that we actually do review the scores with the patients in detail. And we show them the Kaplan-Meier curves that the scores actually reflect. And I think most patients, most of my patients are intensely interested in how their scores – what their scores are and how they change with time. And often at the end of their risk stratification visits, they will ask what their REVEAL score is, because they know the relevance to their one year survival of this. I don’t think any of the patients have come to a point where they’ve actually perseverated and worried about it, but I think it allows them to put their next year in perspective and tells them whether there’s going to be a lot of work that needs to be done this year or this is going to be a good year for me and I can relax a little bit. And so I think it just helps a lot of our patients put their disease into good perspective and allow them to view their next year within the context of what is either a good comfort zone or not a good comfort zone.

Dr Burger: So taking the REVEAL risk score in light of Ioana’s comments about how some of the factors aren’t measured at each visit, specifically the hemodynamics and perhaps the diffusing capacity, are you envisioning continued refinement of risk scoring, perhaps with combination of contemporaneous RV assessment by imaging?

Dr Benza: Oh, absolutely. And that’s just a fantastic question. The calculator was never meant to be the standalone, unalterable tool. And as new clinical tools evolve, the calculator will obviously need to be refreshed, refurbished, with the older factors relooked at, to determine if they hold the same relevance as they did in the past, when these newer tools were not available. And obviously, the biggest addition to the calculator, in my opinion, not only has to include the serial changes in score which give prognostic information, but estimates of – better estimates of right ventricular imaging. You know, in the original evolution of the calculator, many of the qualitative estimates of right ventricular function were significant on a univariate level. But because of the way the registry recorded these data they were very qualitative and so they fell out in a multivariable analysis. But as we get better imaging tools that are more objective, I think these are certainly going to be a great addition to the calculator that can be utilized to quantitate overall risk in conjunction with some of the other stuff that likely will maintain significance. In addition, I think one of the other biggest additions to the calculator that needs to be done is the addition of incremental risk when a decompensation occurs, because as we know and as was beautifully illustrated in some of the literature that came out of REVEAL is that when a patient has a decompensation, that their likelihood of having a mortal or a morbid event in the next six months is extremely high after that event. And so I think that’s an element of risk that certainly needs to be used in conjunction with the score. And in our own group, when we utilize the score, we usually use a three-tier system. So we have the score. And then we try to add to that and put into context their right ventricular imaging. And also whether or not they had or had not had a decompensation. And using that kind of three-tiered decision tree – the score, the imaging, yes or no recent decompensation event – I think those patients’ total risk is depicted more clearly, using a combination of those elements.

Dr Burger: Well, Jonathan and Ioana, how often do you image the RV in your patients that you’re seeing in clinic? And are your decisions swayed by their functional class and their six-minute walk? Or is it something you do routinely?

Dr Rich: Well, I can tell you what I do. And I tend to be pretty aggressive up front in the evaluation and management of the newly diagnosed PAH patient. I think what we don’t necessarily have data for is if we can make patients rapidly better, i.e. as indicated by a significantly improved REVEAL score or by using other markers or indicators of clinical improvement; is that going to project a better long-term outcome than if we take a more “reactive” approach and simply respond to say a worsening in the REVEAL score or other markers, and only then do we layer on or escalate therapies. I tend to be a bit biased in saying, let’s try to make the patient as well as you can, as soon as you can, and be more proactive rather than reactive. And so, I try to utilize everything – with
hemodynamics, a low cardiac output in a young patient who tries to convince me that he’s a functional Class II but his numbers look terrible and his RV looks terrible, I’m really worried about that patient and I would have a very low threshold of going straight to an IV prostanycin to try to get that patient and their RV function as stable as possible. So early on, I think the invasive hemodynamics, coupled with a careful physical examination, imaging, and functional capacity should all be used together to formulate an initial treatment plan. But then moving forward, it’s impractical to be taking patients back to the cath lab on a frequent, regular basis. And so I usually will use simple measures such as how the patient is feeling, are there objective changes in functional capacity, is RV function looking a bit better on echo, which, as Ray pointed out, we’re getting better at in terms of trying to quantify that but it’s still somewhat qualitative and subjective. And then circling back to biomarkers, are we seeing improvements in BNP levels and things like that. You know, if a PH patient told me that it wasn’t long ago that he was playing softball and running the bases and now he can’t do it, I keep pushing the envelope until he tells me he’s getting close to being able to do that again. Even if in some cases it is impractical, I always try to get patients back to as close to their previous baseline as possible, so I might be more aggressive than some. I think it would be nice in some ways actually if we can use calculators such as the REVEAL score and other markers to not only prognosticate whether the patient is more likely to have a difficult year, which is really important like Ray was talking about, but also should we be recalculating these types of scores again really quickly after initiating the initial therapy and if they do not achieve a significant improvement in that score, would that predict the need to escalate more quickly. Because I think we need to be a little more aggressive in most scenarios to try to keep the patient out of trouble rather than waiting until we need to try to get them out of trouble. As Ray said, once they’re decompensated and coming into the hospital, they’re usually in pretty bad shape.

**Dr Burger:** So what does the panel feel the role of exercise is in this whole business of trying to more accurately assess where patients are in their clinical course? Particularly those who fall into the less severe end, if you will, spectrum of functional Class III, where they’re starting to manage their activities of daily living, but, still have exercise limitation with heavy exertion. They’ve made some progress perhaps with some of these other markers that we talked about. But, of course, their symptoms are with exercise and measuring something with exercise might be useful, such as end tidal CO₂.

**Dr Preston:** That’s a good question because typical symptoms for our patients are when they exert themselves. But the markers that bear prognostic value that are derived from the cardiopulmonary exercise test are those that show really bad disease. So by the time they hit those markers, their clinical picture is, I think in my opinion, more obvious, obvious enough that the disease is severe. And we don’t know yet if by improving these markers and to what level that translates into better survival. Nevertheless, in my practice, I use maximal testing, exercise testing, in those young patients in whom, like Jonathan was describing, they seem to underreport their symptoms and they seem to have kind of like a good functional capacity, even though they have severe disease, to better analyze their limitation and their severity of the disease. So younger people, I do exercise them, yes. And it’s just a piece of the puzzle to better understand and determine what’s their disease process.

**Dr Benza:** I guess I use cardiopulmonary exercise testing in people who are reaching their upper limits of clinical predictability in the 6 minute walk test, which is what I use routinely. So if I have a patient who’s still not doing what they think they should be doing but their walks are consistently greater than 400 meters, those people I typically will put on an exercise treadmill and do metabolic testing on them, to see where their perceived dyspnea is coming from, whether it is really an impaired cardiac reserve or impaired ventilatory reserve. And that’s where I’ve found it to be most useful.

**Dr Burger:** Ray, I’ll ask you, because you have recently published in *Advances* a review of ambulatory hemodynamic monitoring. Where do you think the role of ambulatory monitoring devices, CardioMEMS is one example, and the parameters that they would measure are in prognostication and assessment that patients particularly as the conversations always seem to loop back to, are we being aggressive enough with our treatment strategies?

**Dr Benza:** Yeah. Well, I guess this is just as food for thought. I mean, given the rapid and progressive nature of this disease, as I mentioned earlier, I think we continually need to reassess risks, particularly in those who are newly diagnosed and recently decompensated, because they’re the ones who have the most risks. But if you think about it, we’re really limited in our risk prognostication by the number of touch points that we have with our patients. Our patients don’t live with us. We don’t see them every day. So the only time we can risk prognosticate is when they come to clinic or, by chance if we call them on the telephone, are able to assess some sort of factors of their daily disease state from that telephone call. So there’s limitations in touch points that we have, particularly in these people who are at higher risk, I think this really shows us the limitations in our ability to risk prognosticate on a rapid basis, to make sure that these people who are at the highest risk are being treated as aggressively as we want. And as Jonathan mentioned earlier, since hemodynamics really best reflect the status of the disease, the question that’s then begged is, could daily assessments lead to better outcomes, by serving as an early warning signal to identifying decompensation and to augment therapy, I think that’s where the utility of these indwelling hemodynamic monitors will likely be best utilized, at least in the beginning, is to tele-video this group of patients that we
frequently, and that’s usually a direct reflection of the left-sided filling pressures and LV function. But in pulmonary arterial hypertension, it always made me wonder if there could truly be a significant utility in the CardioMEMS device itself, since we think, generally speaking in PAH, that PA pressures, until the disease state gets to a very end stage, probably don’t change much or at least my perception is they don’t change significantly when we bring them back to the cath lab. And the clinical trials seem to support this notion where even after about 12–16 weeks of therapy, the mean change in PA pressure is perhaps around single digits of pressures. Thus, it would almost make me think, what if we could come up with a right atrial pressure monitoring device, similarly to what we have currently with some experimental devices in the left atrium, and perhaps that would actually in some ways be a better marker of fluctuation in patient status. But perhaps the study you are doing with CardioMEMS, which sounds fascinating, will teach us something that we don’t know.

Dr Benza: You bring up a very valuable point. I think this is something that is underappreciated by many of us, in that the right heart catheterization I think lulls us into a false sense of security with some of these patients, because the procedure in part is really artifactual or artificial, in that the patients when we perform these is in supine position and is resting, in the resting state. So what we’ve been able to appreciate with these indwelling devices is that pressures dramatically change with the ambulatory environment, such that when we check ambulatory pressures using this device, there is a significant difference from what we see at rest. And in some patients, that can be the trick in making them feel better, in that we are not or do not have a good sense of whether controlling ambulatory pressures can help these people reduce their morbidity and mortal events that occur throughout their years of observation. And so I think exercise hemodynamics that we get with the use of this device, that you can glean from this device, really open up a whole new avenue of exploration for possible treatment titrations for these people. You know, controlling pressures at rest and with exercise are two totally different things. The other interesting thing with this device is that although not FDA-approved at this point, and we are utilizing this through some algorithms that we have helped develop, is that you can very nicely detect cardiac output with this device, such that you have pressures and outputs and therefore, you can determine resistances and by virtue of knowing that just imagine the other things you can check compliance, that you have pressures in output, RV power. You can do RV stroke work index. So all the parameters that we know are useful when we have a Swan in and we’re managing hemodynamics in the unit, you can get now on an ongoing basis. And so although you don’t have the right atrial pressure, you have strong surrogates of right ventricular function by virtue of knowing the pressure and the outputs. And so these additional things that we are working on and showing that you can do on a long-term basis I think will prove to be very interesting in the future. And obviously, these are not the things that had been reported prior in the literature that you can do with this device but it makes perfect intuitive sense that you can do this. You know, the similar things that we did with the Chronicle device that we utilized a number of years ago, which did give us estimates of right ventricular contractility. So these are very interesting new derivations that you can use, just by virtue of knowing simple pressures and outputs.

Dr Burger: I think this has been a wonderful discussion and particularly enlightening for me personally. I would have the panel, if they’re comfortable, take sort of one final question as we wrap up. And that is, beyond what we discussed, is there anything that you focused on or have seen in the literature and/or participating in study that you would call a novel prognostic indicator?

Dr Ioana: I’d like to mention that hopefully in the near future, we’ll have some biomarkers of inflammation or oxidative stress that we can measure as a whole, the disease process. There’s also some new research on micro-RNAs in
their blood level. And maybe they will become a marker in the future.

**Dr Benza:** One of the things that I'm particularly interested in and trying to do some work in is the predictability of genomics and genetics in determining outcome in patients with this disease state. And I think there is going to be some data that's going to be coming out shortly, hopefully, that will help better identify patients who are at high risk of decompensation or worsening prognosis based on their genetic fingerprints. So I think genetic fingerprints are going to be very helpful I think in the future in pre-identifying people who may have a more aggressive course.

**Dr Burger:** Well, with that, I would like to thank the panel for their very insightful comments. This has been a wide-ranging discussion of an area that's dynamic and critically important to our practice and certainly ripe for new discovery and new refinement of our current ways of evaluating prognosis and response to treatment.
Holistic Assessment of the New Patient With Pulmonary Hypertension: The Role of the Non-Physician Clinician

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Pulmonary hypertension (PH) does not discriminate based on social support, health literacy, emotional bandwidth, or socioeconomic status. Evaluating these factors provides an elemental foundation to best foster the patient's adherence and success. The non-physician clinician plays a pivotal role in assessment of the new patient.

Evaluation of the patient begins with first contact, whether in person, by telephone or records review. This offers a glimpse of the patient's journey. Telephone screening provides insight into the patient's current knowledge base. Understanding when and how the patient learned of his or her diagnosis, the location and results of testing done thus far, and historical treatment attempts identify a point of origin from which to request records, help avoid duplication of evaluation, and lay the foundation for establishing the patient and caregiver as integral members of the PH team, as well as identifying and beginning to fill knowledge gaps. Common practice is to obtain medical records before the appointment, allowing acuity determination to influence scheduling urgency. Additionally, a thorough records evaluation guides the appointment: for example, the conversation with a patient with well documented, severe chronic obstructive pulmonary disease (COPD) is different from that with a patient with PH in the setting of left-sided heart disease and distinctive still from idiopathic PH.

The appointment enables the clinician to gather even more information. Physical assessment, touch, and face-to-face communication help establish a foundation for a healthy, trusting partnership with the PH care team. To accomplish a meaningful encounter, these characteristics should be assessed:

- Ambulation: Can the patient walk unaided? If not, what is the limiting factor? Is it shortness of breath, orthopedic issues, or their footwear?
- Dexterity: Could the patient manipulate a pump? Observe their hands and dexterity. Can they turn the oxygen tank on and off independently? Can they work a remote control? Do they have blisters or ulcers on their fingers? The patient's dexterity may affect abilities to manage infusion or inhalation devices.
- Vision: Is their vision adequate? Do they use glasses or contacts? Are they legally blind? Will they be able to read small screens on devices?, program pumps, or mix medications?
- Hearing: Can they hear well? Do they have hearing aids? Could they hear an electronic alarm?
- Self-care: Is the patient able to care for themselves? Are they well groomed? How are their teeth?
- Social support: Did they come alone to the appointment? Did a family member or friend come with them? Does anyone visit them in the hospital? Lack of self-care can be an indicator of other issues such as depression, financial stability, or disease severity. You may hear “I’m too tired to wash my hair,” or “I feel faint when I shower.” Some therapies are cumbersome to manage and may cause patients to feel overwhelmed. Knowledge of the depth of caregiver support should be considered when choosing the type of therapy. These elements can be observed without ever touching the patient and will help the clinician better understand the patient's needs.

Other considerations should include the following:

- The patient and caregiver's ability to read and write. Printed teaching materials, including charts for daily weight or prostanoid titration schedule, should be provided at the patient's literacy level.
- Potential language barriers should be assessed. Early notification of the patient's primary language helps the specialty pharmacy plan and provide appropriate resources for training, education, and ongoing services, including medication reorders and copayment support.
- Evaluation for medical nonadherence with prescribed medications and treatments: Are medication doses missed? Is the patient wearing oxygen at levels prescribed at rest, with exertion, and sleep? Using prescribed CPAP or BiPAP? Participating in a structured rehab program? Identifying areas of nonadherence is the first step. Next, the clinician should attempt to detect barriers to adherence. Is the patient experiencing side effects? Copay issues? Are self-image, depression, or anxiety being appropriately addressed?

Together, these components will influence the evaluation and management of the patient with PAH. A better understanding of the diagnosis of PAH empowers the patient and their caregivers. An important responsibility of the nurse clinician is the education of patients and caregivers, personalized to
their needs. Quality, up-front education reinforces the patient-center care model and influences conversations going forward.

The nurse clinician plays the role of liaison in the multidisciplinary team, enabling the appropriate contacts between the PH care team, the patient, and their families. The clinician can support patient adherence and recognizes the need for social and psychosocial support. The role of the PH clinician is one that encompasses a variety of skill sets. It is an action role with holistic responsibilities. Even beyond the new patient, the nurse clinician frequently evaluates the process of care and acts as an intermediary between the multidisciplinary team, the patient, and their caregiver. The basis of the initial evaluation shapes the approach to patient care and connects goals and expectations to living with PAH.
In the treatment of pulmonary arterial hypertension (PAH, WHO Group I)

HELP HER WRITE FUTURE CHAPTERS

Once-daily OPSUMIT® (macitentan) is the first and only oral PAH therapy indicated to both delay disease progression and reduce hospitalization for PAH

OPSUMIT is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression.

- Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).
- OPSUMIT also reduced hospitalization for PAH.
- Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years.
  - Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids.
  - Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

IMPORTANT SAFETY INFORMATION

BOXED WARNING: EMBRYO-FETAL TOXICITY

- Do not administer OPSUMIT to a pregnant female because it may cause fetal harm.
- Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.
- For all female patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS).

CONTRAINDICATIONS

Pregnancy: OPSUMIT may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus.

WARNINGS AND PRECAUTIONS

Embryo-fetal Toxicity and OPSUMIT REMS Program

Due to the risk of embryo-fetal toxicity, OPSUMIT is available for females only through a restricted program called the OPSUMIT REMS Program. For females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests.

Hepatotoxicity

- Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 x ULN were 3.4% for OPSUMIT vs 4.5% for placebo, and >8 x ULN were 2.1% vs 0.4%, respectively. Discontinuations for hepatic adverse events were 3.3% for OPSUMIT vs 1.6% for placebo.
- Obtain liver enzyme tests prior to initiation of OPSUMIT and repeat during treatment as clinically indicated.
- Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching).
- If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 x ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT.

Notable requirements of the OPSUMIT REMS Program include:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the OPSUMIT REMS Program prior to initiating OPSUMIT. Male patients are not enrolled in the REMS.
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.
when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Hemoglobin Decrease
- Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and in clinical studies with OPSUMIT. These decreases occurred early and stabilized thereafter.
- In the SERAPHIN study, OPSUMIT caused a mean decrease in hemoglobin (from baseline to 18 months) of about 1.0 g/dL vs no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPSUMIT group vs 3.4% for placebo. Decreases in hemoglobin seldom require transfusion.
- Initiation of OPSUMIT is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated.

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)
Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

Decreased Sperm Counts
Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility.

ADVERSE REACTIONS
Most common adverse reactions (more frequent than placebo by ≥3%) were anemia (13% vs 3%), nasopharyngitis/pharyngitis (20% vs 13%), bronchitis (12% vs 6%), headache (14% vs 9%), influenza (6% vs 2%), and urinary tract infection (9% vs 6%).

DRUG INTERACTIONS
- Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided.
- Strong inhibitors of CYP3A4 like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment.

Please see Brief Summary of Prescribing Information, including BOXED WARNING for embryo-fetal toxicity, on adjacent pages.
INDICATIONS AND USAGE
Pulmonary Arterial Hypertension
OPSUMIT® is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanooids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). OPSUMIT also reduced hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease (12%).

CONTRAINdications
Pregnancy
OPSUMIT® may cause fetal harm when administered to a pregnant woman. OPSUMIT is contraindicated in females who are pregnant. OPSUMIT was consistently shown to have teratogenic effects when administered to animals. If OPSUMIT is used during pregnancy, apprise the patient of the potential hazard to a fetus (see Warnings and Precautions [Embryo-fetal Toxicity] and Use in Specific Populations [Pregnancy]).

WARNINGS AND PRECAUTIONS
Embryo-fetal Toxicity
OPSUMIT® may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable methods of contraception (see Use in Special Populations [Females and Males of Reproductive Potential]).

For all females patients, OPSUMIT is available only through a restricted program called the OPSUMIT Risk Evaluation and Mitigation Strategy (REMS) (see Warnings and Precautions [OPSUMIT REMS Program]).

OPSUMIT REMS Program
For all females, OPSUMIT is available only through a restricted program called the OPSUMIT REMS Program, because of the risk of embryo-fetal toxicity (see Contraindications [Pregnancy], Warnings and Precautions [Embryo-fetal Toxicity], and Use in Specific Populations [Pregnancy, Females and Males of Reproductive Potential]).

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>OPCUMIT 10 mg (N=242)</th>
<th>Placebo (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 x ULN</td>
<td>3.4%</td>
<td>4.5%</td>
</tr>
<tr>
<td>&gt;8 x ULN</td>
<td>2.1%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

In the placebo-controlled study of OPSUMIT®, discontinuations for hepatic adverse events were 3.3% in the OPCUMIT® 10 mg group vs. 1.6% for placebo. Obtain liver enzyme tests prior to initiation of OPSUMIT® and repeat during treatment as clinically indicated. Advise patients to report symptoms suggesting hepatic injury (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching). If clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 x ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT®. Consider re-initiation of OPSUMIT® when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

Hemoglobin Decrease
Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and were observed in clinical studies with OPSUMIT®. These decreases occurred early and stabilized thereafter. In the placebo-controlled study of OPSUMIT® in PAH, OPCUMIT® 10 mg caused a mean decrease in hemoglobin from baseline to up to 18 months of about 1.0 g/dL compared to no change in the placebo group. A decrease in hemoglobin to below 10.0 g/dL was reported in 8.7% of the OPCUMIT® 10 mg group and in 3.4% of the placebo group. Decreases in hemoglobin seldom require transfusion. Initiation of OPSUMIT® is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and repeat during treatment as clinically indicated (see Adverse Reactions [Clinical Trial Experience]).

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)
Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT®.

Decreased Sperm Counts
Other ERAs have caused adverse effects on spermatogenesis. Counsel men about potential effects on fertility (see Use in Specific Populations [Females and Males of Reproductive Potential] and Nonclinical Toxicology [Carcinogenesis, Mutagenesis, Impairment of Fertility]).

ADVERSE REACTIONS
Clinically significant adverse reactions that appear in other sections of the labeling include:

• Embryo-fetal Toxicity (see Warnings and Precautions [Embryo-fetal Toxicity])
• Hepatotoxicity (see Warnings and Precautions [Hepatotoxicity])
• Decrease in Hemoglobin (see Warnings and Precautions [Hemoglobin Decrease])

Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 clinical practice. Safety data for OPSUMIT® were obtained primarily from one placebo-controlled clinical study in 742 patients with PAH (SERAPHIN study). The exposure to OPSUMIT® in this trial was up to 3.6 years with a median exposure of about 2 years (N=429 for 1 year; N=429 for 2 years; and N=98 for more than 3 years). The overall incidence of treatment discontinuations because of adverse events was similar across OPSUMIT® 10 mg and placebo treatment groups (approximately 11%).

Table 2 presents adverse reactions more frequent on OPSUMIT® than on placebo by ≥3%.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>OPCUMIT 10 mg (N=242)</th>
<th>Placebo (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>Nasopharyngitis/pharyngitis</td>
<td>20%</td>
<td>13%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>Influenza</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>9%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of OPSUMIT®. 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.

Immune system disorders: hypersensitivity reactions (angioedema, pruritus and rash) Respiratory, thoracic and mediastinal disorders: nasal congestion
**Drug Interactions**

**Strong CYP3A4 Inducers**

Strong inducers of CYP3A4 such as rifampin significantly reduce macitentan exposure. Concomitant use of OPSUMIT with strong CYP3A4 inducers should be avoided [see Clinical Pharmacology (Pharmacokinetics)].

**Strong CYP3A4 Inhibitors**

Concomitant use of strong CYP3A4 inhibitors like ketoconazole approximately double macitentan exposure. Many HIV drugs like ritonavir are strong inhibitors of CYP3A4. Avoid concomitant use of OPSUMIT with strong CYP3A4 inhibitors [see Clinical Pharmacology (Pharmacokinetics)]. Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment [see Clinical Pharmacology (Pharmacokinetics)].

**Usage in Specific Populations**

**Pregnancy**

Pregnancy Category X.

Risk Summary

OPSUMIT may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Macitentan was teratogenic in rabbits and rats at all doses tested. A no-effect dose was not established in either species. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus [see Contraindications (Pregnancy)].

**Adverse Events**

In both rabbits and rats, there were cardiovascular and mandibular arch fusion abnormalities. Administration of macitentan to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the male fertility of the offspring at all dose levels tested.

**Nursing Mothers**

It is not known whether OPSUMIT is present in human milk. Macitentan and its metabolites are present in the milk of lactating rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions from macitentan in nursing infants, nursing mothers should discontinue nursing or discontinue OPSUMIT.

**Pediatric Use**

The safety and efficacy of OPSUMIT in children have not been established.

**Geriatric Use**

Of the total number of subjects in the clinical study of OPSUMIT for PAH, 14% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

**Females and Males of Reproductive Potential**

**Females**

**Pregnancy Testing**: Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with OPSUMIT and monthly pregnancy tests during treatment with OPSUMIT. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patients on the potential risk to the fetus [see Boxed Warning and Dosage and Administration section 2.2 in full Prescribing Information].

**Contraception**: Female patients of reproductive potential must use acceptable methods of contraception during treatment with OPSUMIT and for 1 month after treatment with OPSUMIT. Patients may choose one highly effective form of contraception (intrauterine devices [IUD], contraceptive implants or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner’s vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see Boxed Warning].

**Males**

Testicular effects: Like other endothelin receptor antagonists, OPSUMIT may have an adverse effect on spermatogenesis [see Warnings and Precautions (Decreased Sperm Count)] and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility).

**Overdose**

OPSUMIT has been administered as a single dose of up to and including 600 mg to healthy subjects (60 times the approved dosage). Adverse reactions of headache, nausea and vomiting were observed. In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because macitentan is highly protein-bound.

**Clinical Pharmacology**

**Pharmacokinetics**

There are no clinically relevant effects of age, sex, or race on the pharmacokinetics of macitentan and its active metabolite.

**Renal Impairment**: Exposure to macitentan and its active metabolite in patients with severe renal impairment (DRI 15-29 mL/min) compared to healthy subjects was increased by 30% and 60%, respectively. This increase is not considered clinically relevant.

**Hepatic Impairment**: Exposure to macitentan was decreased by 21%, 34%, and 6% and exposure to the active metabolite was decreased by 20%, 25%, and 25% in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant.

**Drug Interactions**

**In Vitro Studies**

At plasma levels obtained with dosing at 10 mg once daily, macitentan has no relevant inhibitory or inducing effects on CYP enzymes, and is therefore unlikely to be an inhibitor of the multi-drug resistance protein [P-gp, MDR-1]. Macitentan and its active metabolite are neither substrates nor inhibitors of the organic anion transporting polypeptides (OATP1B1 and OATP1B3) and do not significantly interact with proteins involved in hepatic bile salt transport, i.e., the bile salt export pump (BSEP) and the sodium-dependent taurocholate co-transporting polypeptide (NTCP).

**In Vivo Studies**

**Effect of Other Drugs on Macitentan**: The effect of other drugs on macitentan and its active metabolite are studied in healthy subjects and are shown in Figure 1 below.

**Figure 1**

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Macitentan</th>
<th>Active Metabolite</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>Avoid</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>Avoid</td>
</tr>
<tr>
<td>Ketocazole</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Rifampin</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>Avoid</td>
</tr>
<tr>
<td>Bosentan</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
</tr>
</tbody>
</table>

Effects of other strong CYP3A4 inhibitors such as ritonavir on macitentan were not studied, but are likely to result in an increase in macitentan exposure at steady state similar to that seen with ketoconazole [see Drug Interactions (Strong CYP3A4 Inhibitors)].

**Effect of Macitentan on Other Drugs**

**Warfarin**: Macitentan once daily dosing did not alter the exposure to R- and S-warfarin or their effect on international normalized ratio (INR).

**Sildenafil**: At steady-state, the exposure to sildenafil 20 mg t.i.d. increased by 15% during concomitant administration of macitentan 10 mg once daily. This change is not considered clinically relevant.

**Nonclinical Toxicology**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

**Carcinogenesis**: Carcinogenicity studies of 2 years’ duration did not reveal any carcinogenic potential at exposures 75-fold and 140-fold the human exposure (based on AUC) in male and female mice, respectively, and 8.3- and 42-fold in male and female rats, respectively.

**Mutagenesis**: Macitentan was not genotoxic in a standard battery of in vitro and in vivo assays that included a bacterial reverse mutation assay, an assay for gene mutations in mouse lymphoma cells, a chromosome aberration test in human lymphocytes, and an in vitro micronucleus test in rats.

**Impairment of Fertility**: Treatment of juvenile rats from postnatal Day 4 to Day 114 led to reduced body weight gain and testicular tubular atrophy at exposures 7-fold the human exposure. Fertility was not affected.

Reversible testicular tubular dilatation was observed in chronic toxicity studies at exposures greater than 7-fold and 23-fold the human exposure in rats and dogs, respectively. After 2 years of treatment, tubular atrophy was seen in rats at 4-fold the human exposure. Macitentan did not affect male or female fertility at exposures ranging from 19- to 44-fold the human exposure, respectively, and had no effect on sperm count, motility, and morphology in male rats. No testicular findings were noted in mice after treatment up to 2 years.

**Animal Toxicology**

In dogs, macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of coronary arteries was observed at 17-fold human exposure. Fertility was not affected.

In long-term studies conducted in mice, rats, and dogs, there were no adverse liver findings in long-term studies conducted in mice, rats, and dogs at exposures of 12- to 116-fold the human exposure.

**Manufactured for**: Actelion Pharmaceuticals US, Inc. 1800 South Mathis Court, Ste. 200 South San Francisco, CA 94080, USA


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myPHA: An Online Community for PH Patients and Caregivers

myPHA is the virtual home of hundreds of PH-community members. This online social network allows members to connect with others like them, join in community-wide discussions, explore a customized resource library and more! This a free and comprehensive resource for community connection and empowerment. Signing up is free and easy: www.myPHAssociation.org.

New Exercise Testing Course Available on PHA Online University!

Exercise testing plays a valuable role in evaluating a patient with pulmonary arterial hypertension, especially during the prognostic and diagnostic period. This course discusses cardiopulmonary testing, which is non-invasive and measures a patient’s cardiovascular and respiratory system when undergoing an exercise test. Cardiopulmonary stress tests, functional tests, as well as the administrative oversight needed to execute a successful exercise test will also be highlighted.

This course is accredited for nurses and respiratory therapists at www.PHAOnlineUniv.org/ExerciseTestingNursing and www.PHAOnlineUniv.org/ExerciseTestingRT.

PHA on the Road: PH Patients and Families Education Forums

The Pulmonary Hypertension Association will be on the road again bringing your patients PHA on the Road: PH Patients and Families Education Forums. These free, day-long forums provide education, support and networking opportunities to patients and families living with PH across the country. In 2015, PHA on the Road will be visiting:

- Philadelphia, Pa. on July 25
- Phoenix, Ariz. on October 3
- St. Louis, MO on Oct. 10

If you treat patients living near these regions, please encourage them to learn more and register at www.PHAssociation.org/OnTheRoad.
Up to 15% of people living with scleroderma may be diagnosed with pulmonary arterial hypertension (PAH).²

An online resource designed for people living with PAH

InsightsOnPAH.com

InsightsOnPAH.com was developed to help you learn more about Pulmonary Arterial Hypertension (PAH), including its signs and symptoms, how PAH is diagnosed, options for treatment, and useful tips for living with PAH. A variety of materials are available to download—visit InsightsOnPAH.com to learn more about PAH.


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Program Announcement:

**New Application Deadline:** October 12, 2015  
**Resubmission Deadline:** July 12, 2015  
**New Application Deadline:** February 12, 2016  
**Resubmission Deadline:** November 12, 2015

**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 2013.

**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.

Learn about all of PHA’s research opportunities at [www.PHAssociation.org/MedicalProfessionals/PHAResearchProgram](http://www.PHAssociation.org/MedicalProfessionals/PHAResearchProgram)

* Restrictions apply. Please see complete announcement at the website listed above.
Host a Free PHA On-Demand Event at Your Institution
Bring free PAH medical education to your community. PHA’s On-Demand initiative enables medical professionals to choose a program, topic, speaker, format, and date, and PHA takes care of the rest. Learn more about the On-Demand Program: www.PHAssociation.org/OnDemand.

☐ I would like to receive a quarterly, complimentary copy of Advances in Pulmonary Hypertension.

☐ I would like to receive notification when the online edition of Advances in Pulmonary Hypertension is available.

☐ I would like to receive notification when new PH webinars and online courses are offered.

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Affiliation __________________________
Address __________________________
City __________________________ State ______ ZIP __________
Phone __________________________
E-mail address __________________________
Help Patients Find You!

As PHA strives to better serve our constituents, we are committed to making sure our Find-a-Doctor Directory, available at www.PHAssociation.org/FindADoctor, provides the most up-to-date information for patients. The Find-a-Doctor Directory is PHA’s premier resource for patients seeking PH-treating physicians, and being listed in the directory is a benefit available only to members of PH Clinicians and Researchers (PHCR). To ensure your listing is complete and correct, make sure your online profile is updated. Current members: To update your listing in the Find-a-Doctor Directory, please visit www.PHAssociation.org/PHCR/ProfileUpdate. Lapsed members: To renew your membership, please visit www.PHAssociation.org/PHCR/Renew.