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Research Reviews

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

Overview of WHO Group 2 Pulmonary Hypertension Due to Left Heart Disease
Christopher F. Barnett, MD, MPH; Van N. Selby, MD

The Right Ventricle: A Not-So-Innocent Bystander in Pulmonary Hypertension Due to Left Heart Disease
Brian A. Houston, MD; Steven Hsu, MD; Emmanouil Tampakakis, MD; Ryan J. Tedford, MD

Pulmonary Hypertension Due to Heart Failure With Preserved Ejection Fraction: Clinical Relevance, Management, and Future Directions
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Ask the Expert: Is Cardiac Magnetic Resonance Imaging Underutilized in the Diagnosis of Pulmonary Hypertension?
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Roundtable: Pulmonary Hypertension Due to Left Heart Disease
Teresa De Marco, MD; Brian Shapiro, MD; James Fang, MD; Barry Borlaug, MD; Srinivas Murali, MD
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**General Information**

Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned experts with the oversight of the Association’s Scientific Leadership Council. Its mission is to help physicians in their clinical decision making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in the peer-reviewed literature. Each article is reviewed and approved by members of the Editorial Advisory Board. While most articles are invited by the editorial board, the following submissions will be considered for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics
- Letters to the Editor
- Clinical case studies

Submitted manuscripts are reviewed by the editorial board and other experts in the field. Acceptance of manuscripts is determined by factors such as quality, relevance, and perceived value to clinical decision making.

**Manuscript Preparation and Submission Process**

Submissions should be sent via e-mail as an attached Word document to the managing editor, Deborah McBride, at deb@msspubs.com. Manuscripts should be double-spaced and follow AMA style. Full-length manuscripts should not exceed 4,000 words including references. References should be limited to 50 entries. No more than 5 figures should accompany the manuscript. Acceptable file formats are .gif, .tif, and .jpg. Each figure should be a separate file and figure legends should appear at the end of the manuscript. Each figure should be cited by number in the manuscript. Tables should be self-explanatory and details of the table should not be repeated in the manuscript. Tables should be prepared as part of the Word document. No more than 3 tables should be included with the manuscript. References should conform to AMA style and be numbered consecutively in the text. Reference numbers should be placed in parentheses at the end of the relevant sentence. Accepted manuscripts will be edited for clarity, spelling, punctuation, grammar, and consistency with AMA style.

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The Challenges of Pulmonary Hypertension in Left Heart Disease

Pulmonary hypertension (PH) is a relatively common complication of left heart disease and represents a challenging clinical situation for providers and patients alike. The aging demographic in the United States and widespread use of echocardiography in these patients often results in patients’ being referred for a consult to evaluate the PH. The percentage of patients evaluated in PH centers is sizeable and seemingly increasing. Unfortunately, PH-specific treatment options are limited. The 5th World Symposium on Pulmonary Hypertension concluded that “there is no validated treatment” for PH due to left heart disease. Indeed, there is an argument against use of pulmonary arterial hypertension medications outside clinical trials due to lack of proven efficacy and potential for harm. Regardless, there is a critical need for PH experts to have a thorough understanding of the pathophysiology, clinical presentations, and most appropriate management recommendations. The current issue, guest edited by Dr. Teresa De Marco, offers a wonderful opportunity to review all of those issues in detail.

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References

GUEST EDITOR’S MEMO

Pulmonary hypertension (PH) is a common complication of left heart disease (LHD), often related to severity of the underlying condition. Pulmonary hypertension due to LHD (PH-LHD) is most common in patients with heart failure, with preserved (HFpEF) or reduced ejection fraction (HFrEF), and negatively impacts symptoms, exercise capacity, and outcome. PH-LHD has been recognized as a growing problem in terms of definition, classification, and differential diagnosis; but also for its influence on outcome and therapy. Indeed, distinguishing between pulmonary arterial hypertension (PAH) and HFpEF can be challenging. Compared with PAH, patients with PH due to HFpEF are more often older, female, and have a history of systemic hypertension, atrial fibrillation, and many of the features of the metabolic syndrome. The current hemodynamic definition of PH-LHD combines a mean pulmonary artery pressure ≥25 mm Hg, a pulmonary artery wedge pressure >15 mm Hg, with variable transpulmonary gradient, diastolic pulmonary gradient, and pulmonary vascular resistance depending on the presence of isolated post-capillary PH versus combined post- and pre-capillary PH. However, the hemodynamic definition and the associated terminology have clinical deficiencies and are explored in this issue. Efforts to refine the definition are required and are ongoing. Other than treating the underlying condition, management of PH in LHD remains an unmet medical need lacking an evidence-based approach and any specific approved therapy. The above-mentioned challenges afford an opportunity for a focused review of PH LHD. This issue of *Advances in Pulmonary Hypertension* begins with a comprehensive overview by Drs. Barnett and Selby; followed by a sophisticated discussion of the right ventricle in PH LHD by Drs. Tedford, Houston, Hsu and Tampakakis; a clinically applicable summary of HFpEF with PH by Drs. Cogswell and Thenappan; and ending with a detailed review of valvular heart disease-associated PH by Drs. Horn and Kaple. I congratulate the authors on an outstanding issue of *Advances in Pulmonary Hypertension*.

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Medical Director of Heart Transplantation
UCSF Medical Center
San Francisco, California
NO RIGHT HEART CATH, NO V/Q SCAN, NO DIAGNOSIS

For more information, please visit: www.PHAOnlineUniv.org/DiagnosisTreatment/AboutPH

You already know that the best way to confirm a PH diagnosis is through a right heart catheterization, but are you taking the next step? Every patient with PH should be appropriately screened to rule out the possibility of other types of PH, including chronic thromboembolic pulmonary hypertension (CTEPH). The ventilation/perfusion (V/Q) scan is the preferred and recommended screening test for CTEPH.

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.

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.

Hepatotoxicity

Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the SERAPHIN study >3 × ULN were 3.4% for OPSUMIT vs 4.5% for placebo, and >8 × 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 × 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 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.
Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)

Contraindications (Pregnancy), Warnings and Precautions (Embryo-fetal Toxicity), potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable methods of contraception [see Use in Specific Populations (Females and Males of Reproductive Potential)].

For all female 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)].

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)].

WARNING: EMBRYO-FETAL TOXICITY

• Do not administer OPSUMIT to a pregnant female because it may cause fetal harm [see Contraindications (Pregnancy), Warnings and Precautions (Embryo-fetal Toxicity), Use in Specific Populations (Pregnancy)].
• 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 [see Use in Specific Populations (Females and Males of Reproductive Potential)].
• For all female 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)].

ADVERSE REACTIONS

Hematologic

Anemia 13% 3%

• Hemoglobin Decrease [see Warnings and Precautions (Hemoglobin Decrease)]

In the placebo-controlled study of OPSUMIT, discontinuations for hepatic adverse events were 3.3% in the OPSUMIT 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 × 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.

Lung Effects

Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

Should signs of pulmonary edema occur, consider the possibility of associated PVOD. If confirmed, discontinue OPSUMIT.

Hepatotoxicity

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

Aminotransferases

Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study

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

Table 2: Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>OPSUMIT 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>5%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Further information is available at www.OPSUMITREMS.com or 1-866-228-3546. Information on OPSUMIT certified pharmacies or wholesale distributors is available through Actelion Pathways at 1-866-228-3546.

Hepatotoxicity

Other ERAs have caused elevations of aminotransferases, hepatotoxicity, and liver failure. The incidence of elevated aminotransferases in the study of OPSUMIT in PAH is shown in Table 1.
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)].

USE 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 the fetus [see Contraindications (Pregnancy)].

Adverse Data
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 were 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 years of age 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 (injectable 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)].

OVERDOSAGE
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

Special Populations
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 15-25 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 neither a substrate nor 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 (Point estimate and 90% CI)</th>
<th>Active metabolite (Point estimate and 90% CI)</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</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>Avoid</td>
</tr>
<tr>
<td>Ketocazole</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>Avoid</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>Avoid</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 vivo 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 the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding is considered not relevant for humans.

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:
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South San Francisco, CA 94080, USA
ACT20150219


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With advances in pulmonary hypertension (PH)-specific therapy, the prognosis of pulmonary arterial hypertension (PAH) patients has improved significantly. The National Institutes of Health (NIH) database provided the majority of the data on natural disease progression. The REVEAL database was the second prospective longitudinal observational registry of 55 US sites that compiled data on both incident and prevalent PAH patients, and provided important information on disease progression, prognostic factors, and survival in the new era of PAH therapy. In 2015, 2 articles analyzing the REVEAL database were published: one on 5-year outcomes of patients enrolled in the database and another on prognostic implications of serial risk score assessment.

The REVEAL registry enrolled hemodynamically diagnosed PAH Group 1 patients consecutively from March 2006 to December 2009. Demographics, disease characteristics, hemodynamic data, and management practices data were collected. Prior REVEAL analysis demonstrated that a change in functional class (FC) correlated with survival. For example, worsening from FC III to FC IV predicts worsened survival, and improvement from FC III to FC I/II correlated with improved outcomes. The most recent paper analyzed 5-year survival of both incident and prevalent patients with idiopathic, familial, congenital heart disease, and connective tissue disease—associated PAH, stratified by baseline FC status. Primary survival analysis was conducted for the entire patient cohort (2039 prevalent and 710 incident patients) and the secondary analysis for subgroups (incident vs prevalent patients, age, gender, race, etiology, comorbidities, and baseline clinical characteristics).

The study described the survival rates for the overall patient cohort (with 1-, 3-, and 5-year survival of 90.4%, 76.2%, and 65.4% for prevalent patients vs 86.3%, 69.3%, and 61.2% for 1, 3, and 5 years for incident patients). The poorest outcomes were observed in FC III and IV patients, with incident patients doing better (5-year survival rates of 60.0% and 43.8% vs 57.0% and 27.2% for prevalent patients, respectively). To compare, the NIH database 5-year survival rate was 34% in largely untreated patients, indicating that despite therapy, prevalent patients presenting with FC IV symptoms continue to have a very poor prognosis and probably have a phenotype of the disease less responsive to therapy. In contrast, newly diagnosed FC IV patients represent a mostly treatment-naïve population with greater opportunity for improvement with PAH-specific therapy. Interestingly, FC I and II survival rates were numerically lower in the incident patient cohort (72.0% vs 77.7% in the pooled FC I and II group). This finding is probably due to a better risk profile of prevalent patients in lower FC groups and survivor bias inherent to analysis of pooled incident and prevalent populations. A significant number (30%) of incident FC III patients improved to FC I/II, likely due to administration of PAH-specific therapy within 3 months of diagnosis. This suggests that treatment should be initiated as early as possible in the treatment-naïve patients, as they appear to be at greatest risk of disease progression and probably have the greatest opportunity to experience functional improvement.

When analyzed by etiology, FC at presentation was also strongly associated with 5-year survival in specific etiological subgroups in both incident and prevalent populations, with former subgroups doing better across the subgroups. The study also examined the effect of changes in FC in a subgroup of 1866 prevalent and 614 incident patients within 12 months of enrollment, confirming the results of the previously published data that improvement in FC has a positive impact on outcomes. Another subgroup analysis examined the patients with missing follow-up FC data to determine the effect of other factors on survival and found that white patients has a relatively worse survival, and pulmonary vascular resistance ≤5 Wood units and body mass index >30 provided protective benefit. The authors concluded that single point-in-time FC measurement at enrollment remains an important predictor of outcomes in PAH patients.

To better predict patients’ 1-year survival, the data from REVEAL was used to develop prognostic equation and a simplified risk score calculator and then validated in several studies. The risk score calculator uses 19 clinical variables, widely available in clinical practices, thus making it a useful and simple clinical tool. The authors used the data from the
REVEAL database to assess the prognostic implications of changes in the risk score (increased by at least 1 [or prognosis worsened], unchanged, or decreased by at least 1 [or prognosis improved]), including the contributions of the modifiable variables (such as hemodynamic and vital signs parameters, renal function, 6-minute walk distance [6MWD], brain natriuretic peptide [BNP] level, pericardial effusion status, diffusion lung capacity for carbon monoxide, age, and New York Heart Association [NYHA] FC) during a 12-month period in 2529 patients.

Sixty-seven percent of incident patients started a new PAH therapy, with 35% of patients receiving combination treatment and 25% a prostanoid during the first year. In prevalent patients, new medication was started in 36% of patients, with 54% receiving combination therapy and 34% prostanoids. Numerically, more incident patients had therapy escalation in comparison to their baseline therapy.

At 12 months’ assessment when the risk score was recalculated, 38% had no change, 32% had a decrease, and 30% an increase in the score. The incident or newly diagnosed patients were more likely to improve (or have decreased scores [44%]), in comparison to prevalent patients (28%). Six individual variables improved and/or worsened sufficiently to result in score change: NYHA FC, systolic blood pressure, heart rate, 6MWD, BNP, and presence of pericardial effusion. When patients were stratified by change in risk score, the 1-year survival was 93.7% in patients whose score improved, 90.3% in patients whose score was unchanged, and 84.6% in patients whose score worsened. The findings were similar in both prevalent and incident groups.

The authors examined the effect of risk score at baseline, its change, and the risk score at 12 months’ reassessment as predictors of subsequent 1-year survival in 2 different multivariable Cox models. One analysis demonstrated that the change in risk score significantly predicted subsequent survival (hazard ratio [HR] of 1.67 [95% confidence interval (CI) 1.41–1.99] for worsened score and HR of 0.57 [95% CI 0.47–0.69] for improved score), and another showed that both the enrollment and follow-up risk scores predicted survival with the latter being a stronger predictor of survival (HR 1.40 [95% CI 1.33–1.47] vs HR 1.10 [95% CI 1.04–1.15]), thus underscoring the importance of ongoing risk assessment and aggressive therapy to change modifiable factors. The authors concluded that in addition to clinical assessment, the REVEAL risk score calculator can be used as a prognostic tool serially and help individualize therapy in patients to meet their specific treatment needs.
Overview of WHO Group 2 Pulmonary Hypertension Due to Left Heart Disease

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Background: Left heart disease (LHD) is the most common cause of pulmonary hypertension (PH) and is associated with poor patient outcomes, especially among patients undergoing heart transplant evaluation.

Implications for clinicians: Left heart disease should be considered in all patients undergoing an evaluation for PH. Correct management of PH from LHD is to optimize treatment of LHD. Pulmonary vasodilators used to treat pulmonary arterial hypertension should not be used in patients with PH from LHD.

Conclusions: Additional research is needed to better understand how PH develops in patients with LHD and to investigate the role for treatment targeting PH in these patients.

Left heart disease (LHD) is the most common cause of pulmonary hypertension (PH), and occurs in patients with heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), and valvular heart disease (Figure 1).1,2 The presence of PH in patients with LHD is associated with reduced exercise tolerance and reduced survival, especially following heart transplant.3-10 Identifying LHD as the cause of PH is critically important because it determines the correct approach to management, which is optimal treatment of the underlying LHD with evidence-based and/or standard-of-care pharmacologic or surgical therapies. In patients presenting with PH-LHD, there is currently no role for treatment with pulmonary arterial hypertension (PAH)–specific therapies and, with few exceptions, they should not be administered because they are costly, lack efficacy, and in some cases, are known to increase morbidity and mortality.

NOMENCLATURE, CLASSIFICATION, AND DEFINITIONS OF PH-LHD

The nomenclature that has emerged to categorize patients with PH-LHD attempts to describe the clinical context, pathophysiology, and hemodynamic features seen in these patients. This has resulted in a wide variety of terms used in an effort to accurately describe patients with PH-LHD. Multiple different terms, sometimes used in combination, may be appropriate to describe the unique characteristics of an individual patient with PH-LHD.

Adding to this complexity is changes in terminology that have occurred over time as our understanding of PH-LHD has evolved. Recent guidelines attempted to simplify this language and to classify patients with PH-LHD according to hemodynamic characteristics (Table 1).

The hemodynamic definition of PH is a sustained elevation in mean pulmonary artery pressure (mPAP) ≥25 mm Hg. The usual hemodynamic findings in a patient with PH-LHD are mPAP ≥25 mm Hg in combination with elevated left heart filling pressures, defined as a pulmonary artery wedge pressure (PAWP) >15 mm Hg or left ventricular end diastolic pressure (LVEDP) >15 mm Hg. The clinical characteristics (ie, presence of reduced ejection fraction [EF], clinical features of HFpEF, presence of valvular heart disease) are considered together with the hemodynamic features to arrive at a final diagnosis of PH-LHD.

In patients with PH-LHD, it is important to characterize elevated mPAP as resulting only from passive transmission of elevated left heart filling pressures proximally into the pulmonary circulation vs increased pulmonary arterial resistance resulting from changes in the function and structure of pulmonary arterioles. The terms used to describe patients in whom PH results from transmission of elevated left heart filling pressures include pulmonary venous hypertension and passive PH.

The most recent guidelines recommend using the term isolated postcapillary PH (Ipc-PH) for this group of patients. In these patients, reduction of left heart filling pressures to normal also reduces mPAP to normal.1,11

In other patients, the elevated mPAP is not fully accounted for by passive, proximal transmission of elevated left heart filling pressures. In these patients, it is believed that long-standing elevations in mPAP result in part from vasoconstriction and remodeling of the pulmonary arterioles so that mPAP is elevated out of proportion to the PAWP. Terms that have been used to describe this hemodynamic profile include mixed and out-of-proportion PH. The most recent guidelines recommend using the simple descriptive term “combined postcapillary and precapillary PH” (Cpc-PH).

Differentiating Ipc-PH from Cpc-PH is important because it has prognostic implications, especially in patients undergoing evaluation for heart transplant (Figure 2). Typically, PH-LHD has been characterized by measures of resistance and pressure difference across the
pulmonary vasculature (Table 2). Patients have been considered to have Ipc-PH if the pulmonary vascular resistance (PVR) and transpulmonary gradient (TPG) are normal and Cpc-PH if the PVR and TPG are elevated.

Recent guidelines support the use of the diastolic pressure gradient (DPG) to differentiate the hemodynamic subtypes of PH-LHD. The rationale for this recommendation is that the DPG is less dependent on stroke volume and left atrial pressure, and it was shown to be predictive of survival and correlated with pathologic changes. However, the DPG is subject to error and the association with survival is inconsistent, a reminder that a single measurement is rarely useful to characterize patients with PH.

Vasodilator Testing

Further hemodynamic characterization of Cpc-PH is guideline-recommended in patients with LHD-PH being considered for heart transplantation because it identifies patients at risk for post-transplant right ventricular (RV) failure and death. Vasodilator studies are conducted with a right heart catheter in place. A rapidly acting vasodilator is infused, typically nitroprusside, and measurements of the PVR and TPG are made. Among patients in whom the PVR and TPG are reduced to normal levels while maintaining a systemic systolic blood pressure of ≥85 mm Hg, PH is considered to be reversible or reactive. In these patients post-transplant mortality is similar to patients without PH. Among patients in whom PVR and TPG cannot be reduced to normal, PH is considered not acutely reversible. In many of these patients, the PVR may be lowered or become reversible after prolonged reduction of PAWP with aggressive treatment with diuretics, vasodilators, inodilators, and mechanical support so that patients can become eligible for heart transplantation.

Epidemiology

Accurate prevalence estimates for PH-LHD are limited by factors such as reliance on echocardiographic assessments of pulmonary artery pressure (PAP) to identify affected patients, and inconsistent definitions and cutoffs to diagnose PH-LHD. Studies that make use of gold-standard invasive hemodynamics may be affected by referral bias since sicker patients are likely referred for right heart catheterization (RHC). Even well done invasive studies only provide data at a single time point while the patient is at rest, fasting, and possibly sedated—all of which may affect hemodynamic measurements.

Estimated rates of PH in LHD vary widely. The prevalence of Cpc-PH has ranged from 25% to 47% in hospitalized patients, and was 40% in a recent large ambulatory HFrEF population. Among patients with HFpEF, PH is present in 36% to 83%. A large community study examined echocardiograms from 244 patients with HFpEF and 719 hypertensive controls. Pulmonary hypertension, defined as pulmonary artery systolic pressure (PASP) >35 mm Hg was found in 83% of HFpEF patients compared to only 8% of controls. Using a higher PASP cutoff of 45 mm Hg would have resulted in prevalence of about 50%, a rate similar to that found in another study of 299 patients with HFpEF. A single-center registry of patients undergoing RHC found PH, defined as PVR >2.5 or TPG >12, in 69% of HFpEF patients evaluated. Left-sided valvular heart disease is also commonly associated with PH and is important to recognize because it is an indication for valve replacement or repair. Mitral stenosis is the valvular lesion most often associated with PH, at a rate of up to 73%. Pulmonary hypertension occurs at lower rates in patients with mitral regurgitation (23%–44%) and aortic stenosis (29%–47%).

Prognosis

Compared to patients with LHD and no PH, patients with PH-LHD have
worse outcomes, including worse survival.\textsuperscript{4,27,38-41} This is true in both HFpEF and HFrEF and in studies using both echocardiography and invasive hemodynamics to diagnose PH.\textsuperscript{41} Additionally, survival worsens as PAP increases. A study of patients undergoing endomyocardial biopsy showed a 25\% increase in the risk of death for every increase of 5 mm Hg in mPAP.\textsuperscript{4} Patients with Cpc-PH generally have more severe hemodynamic impairment and worse prognosis compared to Ipc-PH.\textsuperscript{4,10,26}

### PATHOBIOLOGY AND PATHOPHYSIOLOGY

Our understanding of the pathophysiology of PH-LHD has improved in recent years; however, significant gaps remain. It is believed that the first event in the development of PH-LHD is increasing left heart filling pressures and pulmonary venous hypertension. Even when left ventricular (LV) systolic function is normal, diastolic filling abnormalities may result in increased PAP.\textsuperscript{42} Additionally, elevated left heart filling pressures also reduce compliance of the pulmonary vasculature and increase RV afterload by enhancing pulmonary artery wave reflections.\textsuperscript{43} Next, pulmonary arteriolar vasoconstriction occurs secondary to endothelial dysfunction characterized by decreased production of and/or decreased responsiveness to nitric oxide (NO), as well as overproduction of endothelin-1 (ET-1), activation of the renin-angiotensin-aldosterone system (RAAS), and neurogenic activation. Elevated PAPs lead to injury, followed by pathologic remodeling of the pulmonary arterioles including muscularization, medial hypertrophy, and neointimal proliferation.\textsuperscript{44-49} Ultimately the increased afterload imposed on the RV leads to RV systolic dysfunction and failure.\textsuperscript{3,50}

### ASSESSMENT AND DIAGNOSTIC APPROACH

Making a diagnosis of PH-LHD is challenging because symptoms are nonspecific, diagnostic tests can be difficult.
Table 3. Assessment of Left Heart Disease in Pulmonary Hypertension.

<table>
<thead>
<tr>
<th>Initial Tests</th>
<th>Contingent Tests</th>
<th>Favors Primary Contribution of LHD to PH</th>
<th>Favors Alternative Etiology of PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Targeted imaging and serologic evaluation</td>
<td>● Known left ventricular structural disease (eg, MI, cardiomyopathy)</td>
<td>Conditions associated with WHO 1, 3–5 PAH (eg, family history of PAH, BMPR2 mutation, HIV, collagen vascular disease, hemoglobinopathy, portal hypertension, COPD, interstitial lung disease, appetite suppressant or other toxins, previous pulmonary embolism, congenital shunts)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Presence of comorbidities associated with LHD (eg, older age, diabetes, obesity, hypertension)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>● Orthopnea and paroxysmal nocturnal dyspnea</td>
<td></td>
</tr>
<tr>
<td>Physical Exam</td>
<td></td>
<td>● Left-sided S3 or S4 gallop</td>
<td>● Cyanosis, clubbing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Left-sided murmurs (particularly mitral)</td>
<td>● Fine rales, protracted expiration, accessory muscle use, productive cough</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Displaced sustained apical impulse</td>
<td>● Raynaud phenomenon, sclerodactyly, telangiectasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Coarse rales</td>
<td>● Pulmonary vascular bruits</td>
</tr>
<tr>
<td></td>
<td>Exercise ECG</td>
<td>Q waves, left ventricular hypertrophy, left atrial enlargement, left bundle branch block, atrial fibrillation, inducible myocardial ischemia during exercise</td>
<td>Isolated right atrial enlargement and right ventricular hypertrophy, S1Q3T3 pattern</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>Exercise echo</td>
<td>● LV systolic dysfunction</td>
<td>● Isolated right atrial or right ventricular enlargement</td>
</tr>
<tr>
<td>(see Table 4)</td>
<td>Transesophageal echo</td>
<td>● LV diastolic dysfunction</td>
<td>● Intraventricular septum flattening or reverse curvature</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● LV hypertrophy</td>
<td>● Pericardial effusion in the absence of pericardial disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Mitral valve disease</td>
<td>● Congenital disease with shunt</td>
</tr>
<tr>
<td></td>
<td></td>
<td>● Cor triatriatum</td>
<td></td>
</tr>
<tr>
<td>Right heart catheterization</td>
<td>Exercise</td>
<td>● PCWP or LVEDP &gt; 15 mm Hg</td>
<td>● PAP &gt; 25 mm Hg with PCWP &lt; 15 mm Hg</td>
</tr>
<tr>
<td></td>
<td>Vasodilator test</td>
<td>● A abrupt increase in PCWP (to &gt;20–25 mm Hg) with exercise or volume loading</td>
<td>● Exercise PCWP and LVEDP &lt; 20–25 mm Hg</td>
</tr>
<tr>
<td>Volume loading</td>
<td></td>
<td>● Increase PCWP noted during pulmonary-specific vasodilator testing</td>
<td></td>
</tr>
<tr>
<td>Left heart catheterization</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMPR = bone morphogenic protein receptor; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; HIV = human immunodeficiency virus; LV = left ventricular; LHD = left heart disease; LVEDP = left ventricular end-diastolic pressure; MI = myocardial infarction; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; S1Q3T3 = S wave in lead I, Q wave and T wave inversion in lead III; WHO = World Health Organization.


to interpret, and PH may be multifactorial. Consequently, PH-LHD is often incorrectly diagnosed and treated as PAH, especially in elderly patients.\(^{51,52}\) A thoughtful and comprehensive approach to the evaluation of PH is needed so that appropriate treatment can be chosen.

**History and Physical Examination**

Information gathered during a comprehensive history and physical examination is important because it is used to prioritize next steps in the diagnostic evaluation and to provide context for the interpretation of diagnostic testing (Table 3). Details about congenital heart disease, murmurs, valvular disease, HFrEF and HFpEF, and coronary artery disease (CAD), as well as an assessment of risk factors for LHD should be ascertained. Special attention should be paid to factors associated with HFpEF\(^{29}\) such as female gender, advanced age, diabetes, hypertension,
CAD, arrhythmias, and sleep-disordered breathing. Orthopnea and paroxysmal nocturnal dyspnea in a patient with PH strongly suggest the presence of LHD. Physical examination findings that point toward LHD include pulmonary crackles, left-sided S3 or S4, left-sided murmurs, or irregular heart sounds consistent with arrhythmia.

**Diagnostic Studies**

An electrocardiogram and chest x-ray should be performed in all patients undergoing evaluation for PH. Though insensitive and nonspecific, these studies may point to LHD as a cause of PH with evidence of left heart disease such as evidence for myocardial infarction, abnormal heart rhythms, cardiac chamber enlargement or wall thickness, pulmonary edema or congestion, and the absence of parenchymal lung disease.

**Echocardiography**

Echocardiography is the most useful noninvasive modality for the evaluation of PH. It is easy to obtain and may immediately point to LHD as a cause of PH (Table 4, Figure 3). Echocardiographic findings of diastolic dysfunction are well described, but are potentially insensitive for the diagnosis of HFpEF. Therefore, HFpEF should be suspected when findings such as LV hypertrophy and left atrial enlargement are present. In a community-based study of 244 HFpEF patients and 719 hypertensive controls, elevated PAP on echocardiography was both sensitive and specific for the diagnosis of HFpEF, suggesting that the presence of PH on echocardiography is often itself evidence of HFpEF.

Echocardiographic estimation of PASP is the most commonly used method to assess for PH. To estimate the PASP, the tricuspid regurgitant (TR) jet is imaged and interrogated with spectral Doppler in multiple echo windows, and the peak TR jet velocity is determined. The PASP is calculated using the modified Bernoulli equation: PASP = 4(V2) + right atrial (RA) pressure. This technique is limited because it cannot be utilized in patients without an adequate TR jet and spectral Doppler signal. Errors in estimation of PASP may lead to important misclassification of PH.

The shape of the ventricular outflow tract Doppler signal is useful to differentiate patients with PH-LHD. Transient flow deceleration in the right ventricular outflow tract during systole is caused by early return of reflected pulmonary arterial waves, resulting in notched pattern of the Doppler signal. Early wave reflection occurs in the setting of elevated PVR, and notching occurs earlier in systole as PVR increases. Thus, the presence of PH without notching strongly favors a diagnosis of PH-LHD, specifically Ipc-PH. Echocardiography is also useful to assess for RV dysfunction, which is an important marker of increased mortality. Abnormalities of RV size, thickness, and function also provide evidence of clinically significant PH when the PASP cannot be estimated, or indicate that the severity of PH is worse than the estimated PASP suggests. Measurements including RV fractional area change, tricuspid annular systolic plane excursion (TAPSE), tissue Doppler imaging of the tricuspid valve annulus, and strain analysis may all be useful to assess RV systolic function and have prognostic value. These measurements have important limitations so that the overall impression of an experienced echocardiographer is important.

**Magnetic Resonance Imaging**

In patients with suspected PH-LHD, cardiac magnetic resonance imaging (CMR) is useful to detect structural abnormalities of the LV and left atrium, LV systolic function, presence of congenital heart disease, and presence of myocardial fibrosis or infiltrative disease. Similarly, RV enlargement, hypertrophy, and systolic function are best determined by CMR.

**Right and Left Heart Catheterization**

Data from an optimally performed RHC must be incorporated together with the patient’s clinical characteristics and echocardiographic data to arrive at a final diagnosis of PH-LHD. In patients with PH-LHD, data from the RHC are also useful to optimize medical management and are necessary to assess risk in patients being considered for transplantation and mechanical circulatory support. It is crucial that the procedure be performed correctly and that data are properly collected and interpreted.

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Table 4. Distinguishing Pulmonary Hypertension-Left Heart Disease From Pulmonary Artery Hypertension Using Echocardiography.

<table>
<thead>
<tr>
<th>Echo Parameter</th>
<th>Echo Finding</th>
<th>Likelihood of PH-LHD</th>
<th>Likelihood of PAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction</td>
<td>&lt;50%</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Left atrial size</td>
<td>LAD &gt; 40 mm</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>LAVI &gt; 28 mm²</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>LV wall thickness</td>
<td>&gt;11 mm</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Transmural Doppler</td>
<td>Grade II/III diastolic dysfunction</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>Severity &gt; 1x</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>RV size</td>
<td>RV-to-LV area &gt; 1.0</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Intervertricular septum</td>
<td>Systolic flattening</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Interatrial septum</td>
<td>Bowing into LA</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>RV systolic function</td>
<td>TAPSE &lt;1.5 cm</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>RVOT Doppler</td>
<td>Notching</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

LAD = left atrial dimension; LAVI = left atrial volume index; LHD = left heart disease; LV = left ventricular; PH = pulmonary hypertension; RV = right ventricular; RVOT = right ventricular outflow; TDI = tissue Doppler imaging.
A complete hemodynamic assessment includes measurement of RA, RV, pulmonary artery and pulmonary artery wedge pressures, and cardiac output. All pressures should be determined at end expiration during spontaneous breathing to minimize the effects of intrathoracic pressure variation on the measurement. Thermodilution cardiac output measured in triplicate and injected during end expiration remains valid even in the setting of low cardiac output and severe TR.

Incorrect determination of the PAWP may be secondary to many errors, including improper transducer position and zeroing to atmospheric pressure, waveform dampening, incompletely wedged catheter, placement in the RV, measurement that is not at end expiration, and use of the electronic mean obtained from the computer monitor. Mitral regurgitation causes large “v” waves that can be mistakenly interpreted as an elevated PAWP, confounding the calculation of the TPG and DPG. This can be accounted for by reading the PAWP at the time of the “a” wave. Several recent studies have examined the relationship between the PAWP and LVEDP and found that a substantial percentage of patients with PAWP <15 had LVEDP >15, which could lead to misclassification of patients with PH-LHD as PAH. Measurement of the LVEDP should be considered when a reliable PAWP tracing could not be obtained or the value of the PAWP is inconsistent with the expected value based on the clinical picture. Measurement performed manually on pressure tracings at end expiration is most tightly correlated with LVEDP.

**Provocative Testing**
Procedures in the catheterization laboratory are performed while patients are at rest in a fasting state and often after sedating medications have been administered. Hemodynamic findings of LHD...
MANAGEMENT OF PH-LHD
With few exceptions, the appropriate therapy for PH-LHD is optimizing treatment of the underlying LHD. In the case of HFrEF and HfPEF, therapy should include guideline-recommended treatments with diuretics, vasodilators, and neurohormonal antagonists, as well as with device and surgical therapies when appropriate. The benefits of these therapies were emphasized in a recent study showing that adjustment of diuretics and vasodilator agents in response to data from continuous PAP monitoring devices reduced heart failure hospitalizations. Comorbidities that may contribute to PH such as sleep apnea, pulmonary embolism, and chronic obstructive pulmonary disease should also be identified and aggressively treated.

Increased morbidity and mortality associated with PH in patients with LHD makes PH an attractive therapeutic target. However, despite beneficial acute hemodynamic effects and small studies with phosphodiesterase type 5 (PDE5) inhibitors that have shown improvement in exercise capacity, no study has shown PAH therapies to be beneficial in PH-LHD, and some PAH therapies have been associated with significant adverse effects including increased mortality. Most studies of PAH therapies in LHD have not specifically enrolled PH-LHD, so it is possible that undetected benefits will be found in future trials.

Data demonstrating acute hemodynamic improvements including reduced PAWP, PVR, and increased cardiac output provided the rationale for the Flolan International Randomized Survival Trial (FIRST) of epoprostenol in HfPEF. However, the FIRST trial was stopped early when a trend toward increased mortality in the epoprostenol group was identified. Multiple trials of endothelin receptor antagonists for the treatment of HfPEF have been performed and shown either no improvement or worsening edema and hospitalization. Several of these negative studies have never been published.

Phosphodiesterase type 5 inhibitors also have been shown to have beneficial acute hemodynamic benefits including improvements in gas exchange, skeletal muscle function, diastolic function, and RV function; reduced PVR and TPG; increasing cardiac output; improvements in peak oxygen consumption and 6-minute walk; and decreased heart failure hospitalizations. Similar improvements have been shown in patients treated with the soluble guanylate cyclase stimulator riociguat. In clinical practice, sildenafil also decreases PVR and improves RV function after heart transplantation and LVAD implantation.

Despite these encouraging findings, long-term benefits of treatment with these agents have not yet been demonstrated in a randomized controlled trial so that they should not be routinely prescribed in patients with PH-LHD. Additional trials are now underway.

Prolonged treatment with intravenous vasodilators and mechanical support may restore vasodilator response in patients with HfPEF found to have initially irreversible Cpc-PH during heart transplant evaluation. In several reports, LV assist device support has been shown to be effective in reversing PH permitting heart transplant without increased rates of RV failure or death.

CONCLUSION
Much remains unknown about PH-LHD. An improved understanding of triggers and development of vascular changes in PH-LHD as well as the relationship between the LV and the pulmonary vasculature is needed. Failure of studies to demonstrate beneficial long-term outcomes in PH-LHD patients treated with pulmonary vasodilators suggests that PH in this setting may be a marker of severe or inadequately treated left heart failure. Studies that are specifically designed to focus on pulmonary vasodilators in PH-LHD patients with optimally managed LHD are needed.

References


The Right Ventricle: A Not-So-Innocent Bystander in Pulmonary Hypertension Due to Left Heart Disease

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The most common disease associated with high pulmonary vascular pressures and right ventricular (RV) afterload is left heart disease (LHD). In this review, we will discuss the role right heart disease (RHD) plays in LHD progression, prognosis, and treatment. We will first discuss the current definitions employed in RHD and its epidemiology in various left heart diseases. We will next explore the pathophysiology of RV dysfunction in LHD, including a discussion of the effects and components of RV afterload and RV/left ventricular contractile interactions. Finally, we will describe the recently observed clinical implications of RV dysfunction in LHD and pertinent therapeutic considerations.

Contemporary cardiologists have loudly decried the disregard with which the right ventricle (RV) was historically held. In the early 17th century, Sir William Harvey proclaimed, “the right ventricle may be said to be made for the sake of transmitting blood through the lungs, not for nourishing them.” However, between then and the late 20th century, the RV was largely ignored. Indeed, the most striking scientific findings concerning the RV were by investigators who sclerosed the RV in dogs and completely bypassed the RV in humans only to find that circulation continued relatively unimpeded. Thus, the RV was relegated to the status of an innocent bystander in cardiac disease. We now know, of course, that cardiologists of the early 20th century would have been well-served to ask just what the RV was “doing there in the first place.” As cardiac surgery became more prevalent, surgeons began anecdotally noting the importance of right-sided function in predicting patient outcomes during and after surgery. In the 1980s, investigators realized that while a damaged or bypassed RV can support circulation in the face of low afterload, RV function plays an increasingly crucial role in the presence of any disease state associated with elevated afterload. It became clear that with any elevation in afterload, the RV becomes a not-so-innocent bystander.

DEFINITIONS

The International Right Heart Foundation Working Group recently proposed a comprehensive definition of right heart failure as: “a clinical syndrome due to an alteration of structure and/or function of the right heart circu-
Pulmonary Hypertension (PH) is defined by a resting mean pulmonary arterial pressure (mPAP) that is greater than or equal to 25 mm Hg. Mean PAP is a function of the product of cardiac output (CO) and pulmonary vascular resistance (PVR) as well as the downstream left heart pressure (pulmonary artery wedge pressure [PAWP]).

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

Thus, one can see that mPAP may be elevated due to increase in resistance, an increase in flow (CO), or a downstream increase in left heart filling pressure. In cases of LHD, the latter variable predominates, though we will discuss later how it can also contribute to acute and chronic alterations in PVR and capacitance.

The relative contributions of these various components to an elevated mPAP in a given patient carries prognostic and diagnostic information, so considerable attention has been paid to the nomenclature employed to categorize differing hemodynamic profiles.

Recently, the Fifth World Symposium on Pulmonary Hypertension proposed the following: 1) isolated postcapillary PH (IpcPH)—previously termed “passive” PH; and 2) combined postcapillary and precapillary PH (CpcPH)—previously called “reactive,” “out-of-proportion,” or “mixed PH.” IpcPH and CpcPH are differentiated hemodynamically by parameters that suggest a component of pulmonary vascular disease (ie, a precapillary component). Commonly used parameters to differentiate between IpcPH and CpcPH include the transpulmonary gradient (TPG), which is the mPAP minus PAWP, PVR (TPG divided by CO), and the diastolic pulmonary gradient (DPG) (diastolic pulmonary artery pressure (dPAP) minus PAWP) (Table 1). Although initially proposed as the sole discriminator of CpcPH and IpcPH, more recent studies have suggested the DPG may not carry the prognostic significance originally thought, casting doubt on its inclusion in diagnostic definitions.

### EPIDEMIOLOGY

Before delving into the details of right heart disease (RHD) pathophysiology, it is important to identify the extent to which LHD patients are affected by RHD. However, quantification of the prevalence of elevated pulmonary pressure (PH) in LHD carries important caveats. First, most large studies have employed echocardiography in estimating systolic pulmonary artery pressure (sPAP) even though mPAP is the true hemodynamic determinant of the presence of PH. While mPAP can be derived from sPAP with a relative degree of reliability,12,13 echocardiographic measurement of sPAP remains an inexact technique14,15 and requires an adequate tricuspid regurgitation jet. While more precise, retrospective studies employing hemodynamic data are susceptible to referral bias and inadequate fluid optimization status and could overestimate the prevalence of PH in LHD.

Even accounting for these limitations, it is clear that PH in LHD is a prevalent condition. In patients with heart failure with reduced ejection fraction (HFrEF), studies indicate that 26% to 86% of patients have PH.16-19 The prevalence of CpcPH in HFrEF patients ranges from 25% to 47%; a recent evaluation of a large ambulatory HFrEF population found 40% with CpcPH.15 In patients with heart failure with preserved ejection fraction (HFpEF), the prevalence of PH has ranged from 36% to 83%.20-22 Data are more limited on the prevalence of CpcPH in HFpEF. Using a precapillary component definition of PVR >2.5 Wood units or TPG>12 mm Hg, Thenappan found a prevalence of 68% among those patients in their PH registry who had undergone right heart catheterization.23 Given the heterogeneity of HFpEF, vast differences in population demographics present in various publications may also affect the reported prevalence of PH.12,24-25

Finally, PH is prevalent in patients with left-sided valvular disease, including mitral stenosis (up to 73%),26-27 mitral regurgitation (23%–44%),28,29 and aortic stenosis (29%–47%).30-32

### PATHOPHYSIOLOGY OF RHD IN LHD

#### Mechanisms of PH in LHD (Increasing RV Afterload)

In LHD, the inciting abnormality leading to PH is an elevation in LAP, whether due to HFrEF, HFpEF, or valvular disease. This leads to a passive proportional increase in dPAP (and thus mPAP), which results in PH even in the absence of alterations in the pulmonary vasculature.33 However, the pathophysiology is often more complex than simple passive elevation in pressure. Even in the absence of structural pulmonary vascular changes, passive elevations in pulmonary vascular pressure may contribute to a perceived precapillary component to PH. Unlike in the systemic circulation, compliance (or the blood storage capacity of the vessels) in the pulmonary vasculature is more evenly distributed across the pulmonary bed, and the peripheral or distal vessels are responsible for most of the pulmonary vascular compliance.34,35

<table>
<thead>
<tr>
<th>Hemodynamic profiles</th>
<th>IpcPH</th>
<th>CpcPH</th>
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<tbody>
<tr>
<td>PAWP</td>
<td>&gt;15 mm Hg</td>
<td>&gt;15 mm Hg</td>
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<tr>
<td>DPG</td>
<td>&lt;7 mm Hg</td>
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<tr>
<td>TPG</td>
<td>≤12 mm Hg</td>
<td>&gt;12 mm Hg</td>
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<tr>
<td>PVR</td>
<td>&lt;3 mm Hg</td>
<td>≥3 mm Hg</td>
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Table 1.
Thus, the principal determinant of pulmonary vascular compliance is usually PVR, with compliance declining in a predictable hyperbolic fashion as PVR rises. Elevations in left-sided pressure significantly alter this paradigmatic relationship (Figure 1). As passive pressure increases, compliance declines at a given PVR, leading to enhanced pulmonary wave reflections. These reflective waves return during ventricular systole to further increase sPAP. Because dPAP is unaffected by wave reflections, the TPG and PVR increase.

With further elevation in pulmonary pressures, alterations in pulmonary vasoreactivity and structural damage ensue. Smooth muscle vascular relaxation is impaired, likely arising from endothelial dysfunction due to alterations in the nitric oxide, endothelin, and renin-angiotensin-aldosterone signaling pathways. Further, elevated pulmonary vascular pressure results in damage to the pulmonary capillaries. While plexiform lesions (the pathologic correlates of World Health Organization [WHO] Group 1 PH) are notably absent, with sustained injury, deposition of type IV collagen increases, and alterations occur in endothelial cell plasma membranes, cytoskeletal components, calcium handling, and expression of various growth factors. This contributes to physical alveolar-capillary remodeling and impairments in alveolar gas exchange. Further, chronic pressure elevations are associated with increased muscularization of the pulmonary arterioles and medial hypertrophy and neo-intima formation in the pulmonary arteries and veins. All of these changes result in elevations in PVR and a pathologic transition from IpcPH to CpcPH. While improvement in PVR has been described after procedures reducing left-sided pressures (eg, mitral valve surgery, left ventricular assist device), many patients have persistent elevations in PVR, which supports the persistence of these pathologic changes to the PVR. The degree, timing, and prediction of the regression of these
pathologic changes remains poorly understood.

**Response of the RV to Elevated Afterload**

RV afterload is defined by ventricular wall stress occurring throughout ejection. LaPlace’s law defines wall stress ($\sigma$) mathematically as a proportionality between ventricular pressure during ejection ($P_{EJ}$) multiplied by the ventricular radius of curvature ($r_{EJ}$) divided by the wall thickness ($h$).

$$\sigma = \frac{P_{EJ} \cdot r_{EJ}}{h}$$

When considering wall stress, 2 important differences between the LV and RV must be considered. First, the RV is a thin-walled structure, so “$h$” in LaPlace’s equation is a small number even during systole. Second, while the radius of curvature ($r_{EJ}$) declines throughout systole in the LV, mitigating to some extent the increase in pressure, the $r_{EJ}$ declines less (or may actually increase) in the RV during systole. Therefore, RV wall stress is highly dependent on and can be estimated by the pressure ($P_{EJ}$). By integrating the RV systolic pressure over the time between pulmonary valve opening and closing (ejection), one can accurately calculate $P_{EJ}$. Finally, by dividing the end-systolic pressure (ESP) by the stroke volume (SV), one can calculate a validated “lumped” parameter of afterload known as the effective arterial elastance (Ea). In normal subjects, the RV LaPlace relationship described above would predict that RV function would be sensitive to acute increases in pulmonary pressures. Indeed, in a dog model, Abel et al found that an acute increase in mPAP of a mere 10–15 mm Hg resulted in a 30% reduction in right ventricular SV, while a 40 mm Hg increase in mean system arterial pressure only resulted in a 10% reduction in left ventricular SV. This was paralleled in findings by Ghio et al where RV ejection fraction (RVEF) was inversely proportional to mPAP in 377 chronic heart failure patients.

**RV Contractile Adaptation and LV/RV Contractile Interactions**

While the RV is quite sensitive to acute changes in pulmonary pressures, changes may occur over time to improve contractility, matching increases in afterload. While the beat-to-beat adaptation of ventricular contractile function based on preload (heterometric adaptation, described by Starling’s law) is well-appreciated, the RV may also experience augmentation of contractile function with increased afterload conditions (eg, elevated Ea) over time, termed homeometric adaptation and described by Anrep’s law of the heart. In a normal RV, elevations in afterload are matched by homeometric elevations in contractile function and perhaps even adaptive hypertrophy, and the RV and its afterload remain well “coupled.” However, many diseases that affect the left heart respect no septal boundary and may lead to intrinsic RV contractile dysfunction as well. Furthermore, contraction against a chronically elevated afterload leads to adverse RV remodeling (maladaptive hypertrophy, dilation, and ultimately contractile failure). In these cases, RV contractile function cannot augment to match an elevated afterload (it is “uncoupled” from its afterload), and either stroke volume must decline or preload must increase to take advantage of heterometric adaptation to maintain CO.

Finally, it must be understood that the left and right ventricles do not exist in isolation, and are instead highly inter-dependent. In an elegant set of experiments in the early 1990s involving electrically isolated canine ventricles, Damiano et al demonstrated that approximately 30% to 50% of RV contractile energy is generated by LV contraction. More recently, experiments have suggested that septal function is essential for RV longitudinal contraction, which contributes up to 80% of RV systolic function. Therefore, one can appreciate that even in the absence of any intrinsic RV disease, compromise of the LV and/or the interventricular septum (as commonly occurs in LHD) will result in a reduction in the contractile function of the RV.

**CLINICAL AND THERAPEUTIC IMPLICATIONS OF RHD IN VARIOUS LHD STATES**

**Heart Failure**

In a study of 463 patients with HFpEF undergoing hemodynamic catheterization, Miller et al found that the presence of any PH was correlated with an elevated risk of death (adjusted HR 2.24, $P<0.001$). Furthermore, patients with a PVR ≥3 Woods units (termed “mixed PH” in this study) had a significantly elevated risk of death compared with those patients with a PVR <3 (“passive PH”), thus establishing the prognostic import of RV afterload in LHD, and specifically the poor prognosis portended by HF patients with PH and significant precapillary component. Several studies had previously established that HFpEF patients with reduced RV function (defined primarily by echocardiographically derived parameters) carried a worse prognosis. In 2001, Ghio and colleagues studied the additive prognostic value of combining measures of RV afterload (mPAP) and RV systolic function (thermodilution-derived RVEF) in 377 patients with heart failure undergoing hemodynamic catheterization. In this study, patients with elevated mPAP and preserved RVEF comprised a small portion of the population, but had a similar prognosis to patients with a normal mPAP. Patients with an elevated mPAP and reduced RVEF were over 7 times more likely to die or undergo urgent transplantation when compared with patients with normal RVEF and
normal mPAP.\textsuperscript{62} This finding highlights that neither RV function nor pulmonary pressures should be considered in isolation; it is the inability of the RV to remain coupled to its afterload that likely drives disease progression.

For patients with HFpEF, elevated pulmonary pressures carry a worse prognosis as well. In a heart failure cohort with both HFpEF and HFrEF patients, Bursi found increasing tertiles of echocardiographically derived sPAP to be associated with worse survival, independent of LV ejection fraction (LVEF).\textsuperscript{66} In 2014, Melenovsky and colleagues identified RV dysfunction as the strongest predictor of death in an HFpEF population.\textsuperscript{67} Later the same year, Mohammed and colleagues demonstrated that the addition of RV dysfunction (defined by semiquantitative echocardiographic assessment) to elevated afterload carries an increased risk of mortality and hospitalization, similar to HFrEF.\textsuperscript{68}

When considering therapy of RHD in the setting of heart failure, one must remember the contribution of elevated left atrial pressure to RV afterload. As PAWP rises, not only does dPAP passively increase, but pulsatile RV load also increases, leading to out-of-proportion elevations in sPAP, TPG, and PVR as described above. Dupont and colleagues

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Figure 2: Right Ventricular Pressure Volume (PV) Loop from a patient with mild pulmonary hypertension due to heart failure with preserved ejection fraction. The width of the PV loop is the stroke volume (SV; red-dotted line). Due to the shape of the PV loop with pulmonary hypertension, end-systolic pressure (ESP) is closely approximated by peak pulmonary artery systolic pressure. Effective arterial elastance (blue line), a “lumped” parameter of afterload, can then be estimated as systolic pulmonary artery pressure divided by SV.
found that pulmonary artery compliance (estimated as SV/pulmonary pulse pressure) was a better predictor of both RV dysfunction as well as transplant-free survival than PVR. The authors suggested that compliance (like Ea) lumped both resistive (PVR) and pulsatile components into a single measure of RV load. Compliance was also recently shown to predict survival in those heart failure patients with normal PVR.

These studies may suggest that measures of total RV afterload, rather than specifically the precapillary component, are the best hemodynamic predictors of survival in heart failure, and further support the notion that RV function and load influence outcome in left heart failure. Therefore, the importance of adequately treating elevated left heart filling pressures to improve RV afterload and contractile efficiency cannot be overstated. Similarly, therapeutic decisions dependent on measures of RV afterload (eg, heart transplantation for patients with elevated PVR) should only be based on hemodynamics obtained when the left heart filling pressures are optimally treated. To assess and treat RHD in left heart failure, one must first maximally treat the failing left heart.

For patients with continued elevations in RV afterload despite optimization of left heart filling pressures, evidence-based therapeutic options are limited. Given the afterload sensitivity of the RV and the poor prognosis portended by elevated PVR in heart failure, it seems logical that a pharmacologic reduction in the precapillary component of RV afterload would benefit patients with heart failure. Phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil inhibit degradation of cyclic guanosine monophosphate, enhancing signaling through the nitric oxide pathway, and seem tailor-made for therapy of heart failure complicated by RHD. Indeed, early studies showed great promise for sildenafil in both HFrEF and heart failure. However, the RELAX study, a multicenter, double-blind, placebo-controlled, parallel-group, randomized clinical trial of 216 stable outpatients with HFrEF, found that sildenafil did not improve exercise capacity or clinical status compared with placebo. In a substudy of RELAX, Borlaug and colleagues shed light on a potential mechanism of this finding by demonstrating that while sildenafil improved endothelial function and reduced systemic load, it was associated with a reduction in LV contractility and ultimately had no effect on pulmonary artery systolic pressure in these patients.

Other PH-specific pharmacologic agents studied in LHD have met with even more disappointing results. The FIRST study, a multicenter, international, randomized study in 471 HFrEF patients, demonstrated that epoprostenol failed to improve exercise capacity or quality of life and was terminated early due to a strong trend toward decreased survival. Echoing the PDE-5 experience, endothelin-1 antagonists such as bosentan showed early promise in animal and small hemodynamic studies of patients with PH-LHD. However, in the large-scale REACH clinical trial, bosentan therapy failed to improve outcomes and was instead associated with a higher early risk of heart failure events. Importantly, no multicenter randomized study has exclusively enrolled heart failure patients with a significant precapillary component, and it remains unknown if PH-specific therapy could benefit this population.

Recently, Borlaug and colleagues demonstrated the administration of dobutamine (a β-1 agonist) to HfEF patients resulted in improvements in RVEF. Surprisingly, however, they were able to demonstrate that this improvement was solely due to reduction in RV afterload unrelated to reduction in left heart pressures, suggesting that HfEF patients had an underlying reversible pulmonary vasoconstriction that is responsive to β-adrenergic therapy. This suggests a potentially novel direction for pharmacologic therapy for RHD in HfEF patients, though prior experience with β-adrenergic stimulatory therapy in heart failure advises caution.

Left-sided Valvular Disease
Mitrval stenosis represents the paradigmatic left-sided valvular disease associated with the development of PH. Fortunately, correction of the underlying valvular disease usually results in resolution of PH, though improvement may take up to a year to be evident. Young patients with a shorter duration of disease tend to demonstrate more marked improvement, perhaps due to the absence of truly irreversible pulmonary vascular changes. Preoperative severity of PH does not affect outcomes in patients undergoing balloon mitral valvuloplasty, and even patients with very high pulmonary pressures (mPAP >50 mm Hg) may undergo mitral valve replacement surgery with resultant postoperative improvements in pulmonary vascular hemodynamics. Aortic stenosis is also associated with the development of PH, and correction of the underlying valvular disorder is similarly associated with an improvement in pulmonary hemodynamics. Even in patients with severe PH (mPAP >60 mm Hg), recent studies show benefit for aortic valve replacement.

LV Assist Device Therapy
With the growing heart failure population and continued scarcity of suitable transplant organs, left ventricular assist device (LVAD) therapy is becoming increasingly common as both a bridge to transplant and long-term treatment option for end-stage heart failure. While LVAD therapy reduces RV afterload by lowering the left heart filling pressures, up to 40% of patients experience clinical right heart failure after LVAD implantation, and right heart failure is associated with increased mortality post-LVAD. The explanations for the observed RV failure are myriad and include damage to the RV and septum during surgery, disadvantageous changes in ventricular interdependence mitigated by reduced LV contractility, changes in septal architecture, and alterations in RV shape all in the setting of a suddenly elevated CO. Therefore, in patients being considered for LVAD implantation, careful preoperative consideration of RV function is crucial to avoid potentially catastrophic post-LVAD RV failure.

In surgeries involving cardiopulmonary bypass and pericardiotomy (such as traditional LVAD implantation), Raina demonstrated that the RV alters its con-
9. Al-Naamani N, Preston IR, Paulus JK, Hill NS, Roberts KE. Pulmonary Artery Capacitance Is an Important Predictor of Mortality in Heart Failure With a Preserved Ejection Fraction. JACC Heart Fail. 2015(3);467-474.


62. Redfield MM, Chen HH, Borlaug BA, et al;


Pulmonary Hypertension Due to Heart Failure With Preserved Ejection Fraction: Clinical Relevance, Management, and Future Directions

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There are currently 6 million Americans with heart failure, and this number is projected to increase to 8.5 million by 2030. One-half of patients with heart failure have preserved ejection fraction (HFpEF), and the prevalence is increasing. HFpEF can lead to secondary pulmonary hypertension (PH-HFpEF) and is associated with a worsened disease trajectory when present. It is unclear, however, whether PH is a marker of disease severity or a target of treatment in HFpEF. As PH-HFpEF and pulmonary arterial hypertension share several clinical characteristics, the distinction between these 2 syndromes can be difficult. New classification schemes have been proposed to separate those with passive elevations in pulmonary artery pressures from those with more significant pulmonary vascular remodeling. While these classifications have limitations, they are necessary such that pathophysiology, disease trajectory, and pharmacologic therapies can be studied in specific patient subgroups. In this article, we will review the epidemiology of HFpEF, current definitions for both HFpEF and PH in HFpEF, treatment options, and ongoing clinical trials.

Epidemiology of Heart Failure With Preserved Ejection Fraction

The economic cost of heart failure in the United States is estimated to be $24 billion in 2015, and is expected to double to $47 billion by 2030. One-half of patients with heart failure have preserved ejection fraction (HFpEF), and in community studies, HFpEF is now the leading cause of heart failure hospitalization. Increasing age, obesity, metabolic syndrome, female gender, hypertension, and atrial fibrillation are known to be highly associated with development of this syndrome. While historically it has been reported that the prevalence of coronary artery disease (CAD) in HFpEF is lower than heart failure with reduced ejection fraction (HFrEF), recent data suggest that significant CAD can be identified in more than 50% of patients with HFpEF. PATHOPHYSIOLOGY OF HFpEF

The comorbidities that have been associated with the development of HFpEF have been demonstrated to create a systemic pro-inflammatory state. This inflammation then leads to coronary microvasculature inflammation, impairment of endothelial-cardiomycocyte nitric oxide signaling, and production of fibrosis-inducing cytokines. These pathologic changes contribute to myocyte function and myocardial fibrosis, which cause both increased stiffness and abnormal relaxation during diastole. Additionally, left ventricular (LV) systolic function is impaired on echocardiographic strain imaging in HFpEF, suggesting that while the calculated LV ejection fraction (LVEF) is normal, the contractility may be impaired. Patients with HFpEF can also have chronotropic incompetence, abnormal endothelial function, ischemia, pulmonary hypertension (PH), and right ventricular (RV) dysfunction—all of which can contribute to abnormal fluid handling and exercise intolerance. The dominant pathologic finding during exercise can vary from patient to patient.

Definition and Diagnosis of HFpEF

Given the complex pathophysiology and significant heterogeneity within the syndrome, HFpEF can be challenging to diagnose. Comorbidities that also cause dyspnea (obesity, chronic kidney disease, chronic obstructive pulmonary disease) are common in this patient group and may delay the recognition of volume overload. Natriuretic peptides may not be elevated, especially in obese patients and subjects who are clinically stable. As filling pressures are known to fluctuate between times of decompression to euvoeemia, and even from one day to the next, an echocardiogram or right heart catheterization may not reveal elevated filling pressures unless additional maneuvers are performed. Normal filling pressures, therefore, do not exclude the diagnosis. Other conditions that mimic HFpEF but are treated differently need to be considered in the initial evaluation, such as valvular heart disease, infiltrative cardiomyopathies, or constrictive pericarditis. The suspicion of an infiltrative process such as amyloidosis, sarcoidosis, and hemochromatosis is increased when there are clues in the history (carpel tunnel for amyloid, diabetes, or arthritis and family history for hemochromatosis, mediastinal lymphadenopathy for sarcoidosis) or when the echocardiogram, electrocardiogram (ECG), or laboratory findings suggest...
these diagnoses. A septal bounce on echocardiogram with normal natriuretic peptides along with a history of chest radiation, recurrent pericarditis, and prior tuberculosis may indicate that further evaluation for pericardial constriction is warranted.

Because of the complexity of the HFpEF diagnosis, algorithms have been proposed to both unify the definition and help clinicians establish the diagnosis. Guidelines from large cardiology societies vary; however, the European Society of Cardiology proposed that the diagnosis of HFpEF can be made by fulfilling the following 3 criteria: 1) signs and symptoms of heart failure, 2) preserved ejection fraction (LVEF ≥50%), and 3) evidence of diastolic dysfunction either by invasive hemodynamics (left ventricular end diastolic pressure >16 mm Hg or pulmonary artery wedge pressure [PAWP] >12 mm Hg) or by noninvasive myocardial tissue Doppler measures (E/E’ >15). If myocardial tissue Doppler is indeterminate (15 < E/E’ >8), one of the following additional noninvasive diagnostic modalities can be used to diagnose HFpEF: mitral flow Doppler pattern (E/A ratio and deceleration time), LV mass or left atrial volume index, serum N-terminal pro b-type natriuretic peptide (NT-proBNP) or BNP levels, and/or the presence of atrial fibrillation (Figure 1). Additional tools when the PAWP at the time of right heart catheterization is <12 mm Hg include saline loading or exercise. While there is no consensus on the exact pulmonary capillary wedge pressure (PCWP) elevation needed for the diagnosis of HFpEF, it has been suggested that an increase in the PAWP to ≥25 mm Hg with exercise or ≥15 mm Hg with a 1 L fluid challenge is consistent with HFpEF.

**PH IN HFpEF**

Heart failure with preserved ejection fraction and all conditions that cause left-sided heart failure can also cause secondary PH. The most recent World Health Organization (WHO) classification system categorizes PH due to left heart disease into 4 different categories: PH secondary to HFrEF, PH resulting from HFpEF, PH due to left-sided valve disease, and PH associated with congenital/acquired left heart inflow/outflow obstruction and congenital cardiomyopathies. Among these, PH-HFpEF is the most common.

The true prevalence of PH in patients with HFpEF is unknown as the definitions of both HFpEF and PH in HFpEF continue to evolve. Most of the
prevalence data are based on echocardiographic estimation of the systolic pulmonary artery pressure (PAP) rather than invasive hemodynamic assessment. The reported prevalence of PH-HFpEF among the overall HFpEF population varies widely depending on the group studied and the cutoff value of estimated systolic PAP used to define PH. In a population-based study from Olmsted County, Minnesota, 83% of the patients had estimated systolic PAP >35 mm Hg. In a UK-based study of around 350 HFpEF patients referred to a heart failure clinic, only 18% had an estimated systolic PAP of >45 mm Hg.34

Regardless of the underlying left heart pathology, the presence of PH in left heart disease is associated with a worse disease trajectory and overall prognosis. Every 10 mm Hg increase in estimated systolic PAP by echocardiography is associated with a 1.2-fold increased risk of death independent of age. The observed survival in patients with PH-HFpEF may be worse than in those with pulmonary arterial hypertension (PAH) despite having less severe PH and RV dysfunction.

DIFFERENTIATION OF PH-HFpEF AND PAH
Pulmonary hypertension in HFpEF and PAH share several clinical features including signs and symptoms of heart failure and normal LVEF, making the distinction between these 2 entities difficult. The distinction is important as the safety and efficacy of PAH-specific vasodilator therapies is unclear in patients with PH-HFpEF. These therapies have been shown to be either ineffective or to increase mortality in patients with LV systolic dysfunction.35,36

Several clinical, echocardiographic, and hemodynamic characteristics can help differentiate PH-HFpEF from PAH. Compared to PAH, patients with PH-HFpEF are older, more often female, and more frequently have other cardiovascular comorbidities including hypertension, diabetes, obesity, and coronary artery disease.37 In a multivariate model, simple clinical characteristics without echocardiographic or hemodynamic data were able to differentiate PH-HFpEF from PAH with an area under the curve of 0.92. On echocardiography, patients with PH-HFpEF often have left atrial enlargement and less frequently have a midsystolic notching pattern on the RV outflow tract Doppler signal (Figure 2).38 Cardiac MRI derived left atrial volume ≤43 mL/m² can also help to differentiate PH-HFpEF from PAH with an area under the receiver-operating characteristic curve of 0.99.39

On hemodynamic evaluation, patients with PH-HFpEF have only a moderate elevation in PAP and pulmonary vascular resistance (PVR).37 Since the distinction between PAH and PH-HFpEF relies mainly on the accurate measurement of PAWP, meticulous efforts must be made to obtain an accurate PAWP measurement. The wedge pressure should be measured manually at end expiration instead of relying on the digital wedge pressure, and it should be confirmed with a good wedge pressure wave tracing and by checking an oxygen saturation with the catheter in the wedge position (>94% confirms wedge pressure). Partial balloon inflation should be used when overestimation of wedge pressure is suspected due to partial wedging. If the accuracy of wedge pressure measurement cannot be verified, LV end diastolic pressure should be measured by left heart catheterization.41,42

In addition, provocative measures such as saline loading or exercise can help
elicit an abnormal response as patients with the HFpEF syndrome can have a normal resting PAWP or are clinically euvolemic to dry. In a retrospective study of 207 patients, 22% of patients who had PAWP <15 mm Hg at rest were noted to have PAWP >15 mm Hg after 500 cc of acute saline bolus. These patients had very similar clinical, echocardiographic, and hemodynamic characteristics to those with an established diagnosis of PH-HFpEF.

Exercise has also been shown to identify PH-HFpEF in patients with normal resting PAWP. A recent study suggests that exercise may be more sensitive than saline loading for diagnosing PH-HFpEF. A PCWP ≥25 mm Hg with exercise has been suggested to be consistent with HFpEF.

CURRENT NOMENCLATURE
Pulmonary hypertension in HFpEF is defined as mean PAP ≥25 mm Hg in the presence of PAWP >15 mm Hg, signs and symptoms of heart failure, LVEF ≥50%, and absence of significant left-sided valvular heart disease. The cut point of 15 mm Hg for the PAWP in this definition comes from the long-standing definition of WHO Group 2 PH, which splits from an abnormal PAWP at 15 mm Hg. In the European Society of Cardiology algorithm, however, a PAWP of 12 mm Hg or more is needed to diagnose HFpEF. The 12–15 PAWP range remains a gray area but is likely abnormal. With implantable hemodynamic monitoring devices, it is clear that patients who have PAWP <15 mm Hg on one day can change their filling pressures by the next day, suggesting there may be a fair amount of misclassification occurring using our present definitions. Despite these limitations, however, these PH hemodynamic definitions allowed for the advancement of the PH field and for the dramatic improvement in survival that has been observed. This is also why such effort is currently being put forth to try to further classify PH in left heart disease such that meaningful subgroups with shared pathophysiology can be identified.

The working definitions of PH in left heart disease will be reviewed here. Pulmonary hypertension due to left heart disease including PH-HFpEF is classified into 2 broad categories depending on the presence or absence of intrinsic pulmonary vascular disease, otherwise known as the “precapillary” component. These definitions presently rely on a few key invasive hemodynamics variables defined in Table 1.

<table>
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<th>Abbreviation</th>
<th>Long Terminology</th>
<th>Definition</th>
<th>Normal Values</th>
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<tbody>
<tr>
<td>PAM</td>
<td>Mean pulmonary artery pressure</td>
<td>(PA systolic pressure + 2[PA diastolic pressure])/3</td>
<td>&lt;25 mm Hg</td>
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<td>PAWP</td>
<td>Pulmonary artery wedge pressure</td>
<td>A surrogate of left-sided filling pressures</td>
<td>&lt;12 mm Hg</td>
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<td>TPG</td>
<td>Transpulmonary gradient</td>
<td>PAM – PAWP</td>
<td>&lt;12–15 mm Hg</td>
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<td>PVR</td>
<td>Pulmonary vascular resistance</td>
<td>TPG/cardiac output</td>
<td>&lt;2.5–3 Wood units</td>
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<td>DPG</td>
<td>Diastolic pulmonary gradient</td>
<td>PA diastolic pressure – PAWP</td>
<td>&lt;7 mm Hg</td>
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*A cut point of 12 mm Hg is used for PAWP based on the most current consensus definition of HFpEF by the AHA/ACC.

**ISOLATED POSTCAPILLARY PH-HFpEF**
Isolated postcapillary PH-HFpEF is characterized by passive increase in PAP without significant pulmonary vasoconstriction or remodeling of the small pulmonary arteries. Due to the absence of a precapillary component, the increase in PAP is proportional to the increase in the left-sided filling pressure and therefore normalizes completely with a reduction in the left-sided filling pressure. At this stage, due to the absence of a precapillary component, both the transpulmonary gradient (TPG: the difference between mean PAP and PAWP) and the PVR typically remain within normal limits (TPG <12–15 mm Hg and PVR <2.5–3 Wood units). However, both TPG and PVR have been demonstrated to be flow-dependent and may not accurately reflect the presence of intrinsic pulmonary arteriolar remodeling. As DPG is not flow-dependent, this has been proposed as a superior measure of the precapillary pulmonary arteriolar remodeling. Hence, at the most recent Fifth World Symposium on PH, new classification and hemodynamic definition for PH due to left heart...
disease was proposed based on DPG: isolated postcapillary (mean PAP ≥ 25 mm Hg, PAWP > 15 mm Hg, and DPG < 7 mm Hg) and combined postcapillary and precapillary PH (mean PAP ≥ 25 mm Hg, PAWP > 15 mm Hg, and DPG ≥ 7 mm Hg). Since this nomenclature was put forth, however, the DPG variable has not performed well as a prognostic marker, calling into question the clinical utility and repeatability of DPG in real-world practice.

LIMITATIONS OF CURRENT DEFINITIONS
Some speculation as to why the DPG may not be as reliable as an indicator as initially hoped for is due to the low absolute number of this measure, which increases its susceptibility to measurement error and its variability with heart rate. Dichotomization at one specific point to split normal from abnormal also leads to loss of information and misclassification. Some of these limitations, however, apply to all hemodynamic definitions. Whether or not hemodynamic classification by DPG will be clinically meaningful remains to be proven. It may be that optimal classification will include hemodynamic variables after provocative testing, repeated hemodynamic measures over time, and perhaps clinical variables as well.

The take-home point regarding the current nomenclature is that “mixed PH” is suspected when the PVR, TPG, and/or DPG is elevated beyond what would be expected for passive congestion only and not corrected with acute PAWP reduction in the catheterization lab: these are the patients for whom pulmonary vascular pathology is likely. In addition, a PAWP of ≥ 12 is likely abnormal and in the right clinical context is consistent with HFpEF.

TREATMENT
Presently, the management of PH-HFpEF consists of treating the underlying HFpEF. While guidelines for HFpEF treatment support diuretics and systemic blood pressure control, no specific therapies have been demonstrated to decrease mortality or reduce heart failure hospitalizations in a large randomized clinical trial. Spironolactone was recently shown to decrease hospitalization in patients with HFpEF; however, there was no effect on mortality.25 Revascularization in patients with HFpEF and concomitant significant CAD was associated with preservation of ejection fraction and a reduction in mortality in one retrospective single-center study. While this was not a randomized clinical trial, it underscores the importance of evaluating for ischemia if within the goals of care.

ROLE OF PULMONARY VASODILATOR THERAPIES IN PH-HFpEF
Pulmonary arterial vasodilator therapies improve functional capacity, time to clinical worsening, and survival in patients with PAH. The efficacy of PAH-specific therapies in PH-HFpEF is unclear, and there is a theoretical concern that these therapies may cause worsening pulmonary edema by increasing pulmonary blood flow in the presence of elevated left-sided filling pressures.35-37 Endothelin receptor antagonists and parenteral prostacyclin (intravenous epoprostenol) therapy have been shown to be either neutral or increase mortality in patients with LV systolic dysfunction.38,39 Only a limited number of clinical trials have thus far evaluated the safety and efficacy of pulmonary arterial vasodilator therapies in PH-HFpEF. These trials are either neutral or small single-center studies; therefore, PAH-specific therapies are currently not approved for the treatment of PH-HFpEF.

Phosphodiesterase Type 5 Inhibitors
Of all the various PAH-specific therapies, phosphodiesterase type 5 (PDE5) inhibitors have been studied the most in PH-HFpEF. In a single-center randomized clinical trial, 44 patients were randomized to either placebo or sildenafil 50 mg 3 times per day for 12 months.24 Cardiac hypertrophy and elevated DPG (~ 9 mm Hg) were required for trial entry, consistent with combined post- and precapillary PH in the setting of HFpEF. After 6 months, there were significant improvements in RV function as demonstrated by decreased right atrial pressure (10.6 ± 3.6 mm Hg vs 22.0 ± 5.2 mm Hg), increased tricuspid annular plane systolic excursion (19.2 ± 2.3 mm vs 10.6 ± 2.3 mm), and increased RV mean systolic ejection rate (276 ± 25.1 mL/s vs 231 ± 24.2 mL/s) in the sildenafil-treated group compared to placebo. There were also significant changes in the pulmonary vasculature as mean PAP (22.3 ± 3.7 mm Hg vs 37.8 ± 4.9 mm Hg) and PVR (1.18 ± 0.50 Wood units vs 3.42 ± 1.02 Wood units) decreased significantly with sildenafil therapy compared to placebo at 6 months. The beneficial effects of sildenafil persisted at 12 months and sildenafil was associated with improvement in quality of life. Collectively, these data suggest sildenafil may be a useful treatment in PH-HFpEF patients. However, this study did not include hospitalization for heart failure or mortality given its small size. It is unclear whether these hemodynamic and echocardiographic improvements will translate to a meaningful clinical improvement.

In contrast, the positive effects of sildenafil were not observed in the RELAX study, a multicenter clinical trial that assessed sildenafil in HFpEF patients.56 Pulmonary hypertension was not required for trial entry and the trial did not specifically investigate pulmonary hemodynamics and RV function. Another trial assessing sildenafil in PH-HFpEF has recently been completed in Germany (NCT01726049) and the results are pending. This trial will determine how 12 weeks of treatment with sildenafil affects invasive hemodynamics and peak VO2.

Soluble Guanylate Cyclase Stimulators
The DILATE-1 trial assessed riociguat, a soluble guanylate cyclase activator, in the PH-HFpEF population.56 DILATE-1 compared varying doses of riociguat: 0.5 mg in 8 patients, 1 mg in 7 patients, and 2 mg in 10 patients compared to placebo (in 11 patients) to determine the short-term effects on invasive hemodynamics 6 hours after administration of the study drug. There was no difference in the change in mean PAP between baseline and 6-hour time
Endothelin Receptor Antagonists

In a randomized placebo-controlled trial of 192 patients, 6 months of sitaxsentan, a selective endothelin A receptor antagonist, treatment improved treadmill exercise time compared to placebo (90 seconds vs 30 seconds). However, there was no change in LV mass or trans-mitral diastolic parameters. The presence of PH was not a prerequisite for inclusion in this trial, and the effect of sitaxsentan on pulmonary hemodynamics was not assessed. The BADDHY trial is assessing the impact of 12 weeks of bosentan treatment on 6-minute walk test, hemodynamics via echocardiography, and symptomatic burden (NCT00820352).

CONCLUSION

In summary, the incidence of HFrEF is increasing rapidly. The diagnosis can be difficult to make and the definition of the HFrEF syndrome is still evolving. Pulmonary hypertension secondary to HFrEF is very common and associated with a worsened disease trajectory when present. Treatments targeting not only HFrEF but also PH associated with HFrEF are urgently needed. The classification scheme describing the various hemodynamic profiles of PH related to left heart disease has limitations, but has recently evolved to try to help categorize patients in meaningful ways. Several novel treatments for PH-HFrEF and HFrEF are currently being tested, giving hope to the prospect of new treatments for these challenging syndromes in the near future.

References

Pulmonary Hypertension Due to Valvular Heart Disease: Aortic and Mitral

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Pulmonary hypertension (PH) can be due to a primary pulmonary vasculature abnormality, but is more often secondary to lung, cardiac, or environmental insults, and is frequently multifactorial. Most commonly, left heart disease is at fault, a subset of which is valvular heart disease (VHD). With sufficient time, most chronic left-sided valve lesions will result in some element of PH. Long-standing PH causes pulmonary vascular remodeling and progressive PH due to reduced vascular compliance. Careful monitoring of VHD progression is critical, both through screening imaging and patient education, in order to properly time intervention to prevent the development or worsening of PH. The primary diagnostic tool in PH due to VHD is echocardiography, while invasive hemodynamic evaluation can be helpful to determine PH etiology or severity when echocardiography is not adequate. The presence of PH in VHD is often an indication for intervention, but it also increases procedural risk. Severe PH, however, has not been proven to preclude safe intervention, but rather should prompt full preprocedural evaluation and close intra- and postprocedural monitoring. Valve replacement or repair can be viewed as a treatment for PH secondary to the valvular lesion. Percutaneous alternatives to surgical interventions are available for some mitral and aortic valve conditions. Though in relatively early stages of development, these less invasive procedures may improve the safety profile of valve interventions. Pulmonary hypertension that fails to improve after intervention should raise suspicion for procedural failure or underlying pulmonary vascular disease (either precapillary possibly in association with interstitial lung disease or scleroderma or secondary to combined pre-/postcapillary PH due to long-standing pulmonary venous hypertension). This review is focused on the pathophysiology, treatment options, and outcomes in patients with PH due to mitral and aortic valve lesions.

PREVALENCE AND PATHOPHYSIOLOGY
Pulmonary hypertension (PH) due to left-sided heart disease (LHD), classified by the World Health Organization as Group 2 (WHO 2), is secondary to left ventricular (LV) systolic dysfunction (heart failure with reduced ejection fraction – HFrEF), LV diastolic dysfunction (heart failure with preserved ejection fraction – HFpEF), or valvular heart disease (VHD). The principle insult in this class of PH is elevated left ventricular end diastolic pressure (LVEDP, and/or left atrial pressures), which is transmitted to the pulmonary vasculature, raising pulmonary artery pressure (PAP). This PH physiology is postcapillary and defined as a mean PAP (mPAP) ≥25 mm Hg and the pulmonary capillary wedge pressure (PCWP) is >15 mm Hg. Other hemodynamic features of postcapillary PH include increased left atrial pressure (>15 mm Hg) and/or increased LVEDP (>15 mm Hg). When the difference between mPAP and PCWP (known as transpulmonary gradient, TPG) is ≤12 mm Hg, pulmonary diastolic gradient (PDG) <7, and/or the pulmonary vascular resistance (PVR) is <3 Wood units, the elevated PAP is attributable to left heart disease and is considered passive pulmonary venous hypertension. If the TPG is >12 mm Hg or the PVR is ≥3 Wood units, the PH is described as combined precapillary-postcapillary PH (CPpPH). This previously described “postcapillary reactive” or exaggerated PH can have a variety of mechanisms and comorbidities, particularly in the aging population. Most often, this is due to long-standing pulmonary venous hypertension causing significant vascular remodeling and decreased pulmonary circulation compliance. Repetitive and sustained injury to the pulmonary vasculature results in pathologic changes at the cellular level (increased neurohormonal feedback, endothelin-1 and cytokine activation, decreased nitric oxide and brain natriuretic peptide). But complicating the primary insult of pulmonary venous hypertension, other common comorbidities include: lung disease that can be abnormal lung physiology from sleep apnea, aging-related decreased lung function, anemia, atrial fibrillation, and renal failure may all play a role in the combined pre-/postcapillary phenotype.
WHO 2 PH – HFrEF, an independent risk factor for increased mortality in HFrEF, is an essential part of the evaluation with respect to pulmonary vascular reactivity for heart transplant. In this population, PH may be reversible with appropriate use of a durable left ventricular assist device (LVAD) to improve the left-sided hemodynamics and lead to reversibility over several months. WHO 2 PH in HFrEF may be more complicated given that the disease itself includes different phenotypes. The disease is often multifactorial, with mixed etiologies and needing a multidisciplinary approach to address treatable underlying causes. Pulmonary hypertension in VHD requires careful analysis to choose the right patient for appropriate valvular interventions inasmuch as valvular repair/replacement is the treatment of choice for the valvular-related WHO 2 PH.

Aortic and mitral valve disease, both insufficiency and stenosis, can lead to the downstream development of PH. The prevalence of PH-VHD is difficult to determine due to varying cutoff values and methods of assessment in the published literature. Furthermore, limitations of echocardiographic and invasive hemodynamic measurements of PAP add further limitations. Echocardiography may over- or underestimate PAP and requires an adequate jet of tricuspid regurgitation (TR), while invasive measurements are often subject to referral bias. Elevated PAP has long been recognized as a complication of mitral stenosis (MS). Hart et al reported 73% of 317 patients with severe MS undergoing percutaneous mitral balloon valvuloplasty (PMBV) had mPAP >25 mm Hg. Roughly two-thirds of patients with severe aortic stenosis have PH. By comparison, the development of PH in mitral regurgitation (MR) is dependent on the valvular abnormality and chronicity. Barbieri et al demonstrated that degenerative MR due to a flail leaflet causes PH at baseline in 23% of patients. The prevalence of PH in functional MR is up to 44%, and is dependent on LV loading conditions as well as left atrial compliance and function. Patients with a greater amount of MR are more likely to have PH, as demonstrated in a cohort study of 1541 patients with HFrEF. This study also demonstrated that patients with a pre-capillary component to PH or worse LV diastolic component to PH or worse LV diastolic dysfunction had more severe MR.

### Assessment

A new diagnosis of PH should prompt a detailed evaluation of the left heart, including assessment of valvular function. One should obtain a detailed history, focusing on risk factors for LHD (assessment for risk factors, prior congenital heart disease, known cardiac murmurs or valvular heart disease, coronary artery disease) and symptoms (especially effort tolerance, orthopnea, and paroxysmal nocturnal dyspnea). Physical examination findings for right heart failure due to PH are often non-specific (edema, hypotension, elevated jugular venous pressure, loud pulmonic valve closure, right ventricular lift, rightsided S3). Signs of pulmonary edema and an audible S3 or S4 are more specific for LHD. Cardiac auscultation for classic findings of aortic and mitral pathologies should be performed, the specifics of which are beyond the scope of this review. Electrocardiography can be useful to demonstrate chamber enlargement and identify conduction and rhythm abnormalities, though most findings lack sensitivity for valvular pathologies. Chest radiography with an x-ray or computed tomography (CT) will help demonstrate pulmonary edema, chamber enlargement, and potentially valvular calcification.

Echocardiography is the primary diagnostic tool for valvular heart disease, as it is a cost-effective method with high sensitivity and specificity, providing both structural and hemodynamic information. Pulmonary artery systolic pressure (PASP) can be calculated using the modified Bernoulli equation (PASP=4*v[tricuspid regurgitation jet velocity]^2 + right atrial pressure). This method can over- and underestimate PAP, and requires a high-quality Doppler signal from an adequate TR jet, which has been reported to be lacking in up to 89% of ambulatory heart failure patients. Agitated saline contrast can be used to determine the presence of shunts, which are not uncommon in the setting of PH or congenital heart disease. Provided there are adequate acoustic windows, echocardiography allows for accurate assessment of mitral and aortic stenosis and regurgitation (both of native and bioprosthetic valves using M-Mode, 2D and 3D imaging). Standardized and validated definitions for MS, MR, aortic stenosis (AS), and aortic insufficiency (AI) are provided through the American Society of Echocardiography. Echocardiography also allows for evaluation of endocarditis lesions, which can cause significant valvular regurgitation. Mode of failure of bioprosthetic valves can be determined by echo, such as regurgitation (perivalvular or central), valve dehiscence, or stenosis (leaflet immobility, calcification, or patient prosthesis mismatch).

Cardiac magnetic resonance imaging (CMR) is an expensive tool, but can provide accurate assessment of valvular regurgitation (including regurgitant fraction), chamber size and function, jet velocities through stenotic valves, and congenital heart disease. Given that transthoracic echocardiogram (TTE) can underassess severity of MR, in the right patient cohort, use of either CMR or transesophageal echocardiogram (TEE) is often recommended to detect more significant regurgitation.

Invasive right heart catheterization (RHC) with a balloon-directed pulmonary artery catheter is the gold standard for determining PAP. When combined with echocardiographic data, invasive hemodynamics can help differentiate the etiology of PH, which is often multifactorial. Provocative testing (exercise and fluid challenge) and vasodilator testing can be performed as well to help isolate the pre- and postcapillary components of PH and determine the true PH etiology. Data from RHC can also be useful in optimizing medical therapy in PH-VHD. Pressures in each chamber (right atrium, right ventricle, and pulmonary artery) and PCWP should be taken at end expiration in spontaneously breathing patients. Fick cardiac output (CO) or thermodilution CO should be calculated, the latter being the preference in low CO patients. The PCWP tracing in MR demonstrates...
tall V waves, representing the transmitted wave of pressure, which occurs during LV systole. Direct LV pressure measurement should be considered if PCWP is not reliable or yields an unexpected finding. When echocardiography findings are incongruent with clinical findings of MS or AS, one should consider invasive measurement of transvalvular gradients.

**MANAGEMENT**

**General Comments**

Treatment for PH-LHD should begin with guideline-directed pharmacologic treatment for the underlying HFrEF and HfPEF: diuretics, vasodilators, and neurohormonal antagonists. In addition, patients should be considered for mechanical support and resynchronization therapy when appropriate. Targeted therapies for PH-LHD are lacking, showing only limited benefit in symptomatic improvement without affecting clinical survival. However, the subset of PH due to VHD is an exception: surgical and percutaneous interventions for underlying valvular lesions have a meaningful impact on improving PH.

The development of PH is often an indication for mitral valve (MV) or aortoventricular (AV) intervention, but has also been well documented to be a procedural risk factor. Interventions for VHD include surgical approaches, but percutaneous approaches are rapidly being adopted for patients who are high or prohibitive risk for surgery (often elderly patients with multiple comorbidities). The postcapillary component of PH will improve after valve intervention. The degree to which the precapillary component of PH (due to pulmonary vascular remodeling secondary to long-standing PH) can improve after intervention remains unpredictable. Patient prosthesis mismatch after valve replacement (especially after MV replacement) must be considered as a cause of persistently elevated PAP.

**Mitral Stenosis**

Severe MS will result in left atrial hypertension and some degree of PH over time, often in the severe range. Roughly three-fourths of patients will have mPAP >25 mm Hg at the time of PMBV, and one-quarter in the severe range (defined by PVR >6 Wood units). Pulmonary hypertension in the setting of MS appears to be a function of poor atrial compliance (defined as (MV area, MVA)/(mitral E wave downslope) <4 mL/mm Hg), which is in turn a predictor of worse functional capacity and the need for MV replacement or repair. Early concerns for predictable and durable improvement of PH after MV surgery were addressed by Braunwald et al, who reported full pre- and postoperative hemodynamic changes in a cohort of 31 patients. This pivotal trial showed an improvement in PVR (543 to 243 dynes-s-cm²) and increased pulmonary blood flow in patients with MV repair for mitral stenosis. Severity of MS is based on mean gradient, PASP, and valve area (severe range: mean gradient >10 mm Hg, PASP >50 mm Hg, and MV area of <1.0 cm²). Estimated 5-year survival for unrepaird symptomatic MS is 44%. Echocardiographic assessment will demonstrate severity of obstruction, leaflet mobility, thickening, calcification, and subvalvular involvement, all of which are used to calculate the Wilkins score. Symptomatic (New York Heart Association [NYHA] functional class II) patients with a Wilkins score <8 and less than moderate MR can be considered for PMBV. Patients with asymptomatic moderate or severe MS can be considered for PMBV with resting PASP >50 mm Hg, or exercise-induced PASP >60, PCWP >25 mm Hg, or MV gradient >15 mm Hg. Successful PMBV is defined as increasing MVA to 1.5 cm² or ≥50% increase in MVA with <3+ MR. Freedom from death, repeat PMBV, or MV replacement is 50% to 65% at 3–7 years (80% to 90% with the most favorable valve morphology). The most comprehensive assessment of the impact of PMBV on PH due to MS included 559 patients by Fawzy et al. This study demonstrated that PMBV achieved modest immediate reduction in PAP, but normalization of PAP at 6 and 12 months follow-up regardless of pre-PMBV PH severity (mild: 40 ± 13 to 28 ± 8 mm Hg, moderate: 54 ± 17 to 31 ± 9 mm Hg, severe: 92 ± 17 to 29 ± 5 mm Hg). Open or closed MV commissurotomy surgical repair for MS continues to have a role in patients who are not candidates for or who have failed PMBV. Freedom for reoperation with closed commissurotomy is 50% at 15 years. Mitral valve replacement is reserved for those who require surgery with unsuitable anatomy for repair. Operative mortality for MV replacement is 5% to 20%, and correlates with degree of PH (as well as age, functional class, and coronary artery disease). There is great interest in developing a transcatheter MV replacement platform, and several are in feasibility and early in–man stages.
tension in the setting of functional MR increases mortality, even when controlling for the degree of LV dysfunction. Acute severe MR is rare, but most often occurs due to ruptured chordae with or without underlying endocarditis. Acute onset MR results in rapid increase in pulmonary venous pressure and pulmonary edema, often accompanied by systemic hypotension and tachycardia aimed at compensating for acute reduction in afterload.

Medical treatment for chronic degenerative MR is aimed at lowering LV afterload (angiotensin-converting enzyme inhibitor, ACE; or angiotensin receptor blockers, ARB), but has not been shown to reduce clinical event rates. On the other hand, there is a well-established survival benefit with guideline-directed therapy for chronic functional MR due to LV systolic dysfunction or ischemic cardiomyopathy. These medications include ACE/ARB, beta-blockers, and treatment for coronary artery disease when applicable. Cardiac resynchronization therapy with biventricular pacing should also be considered in patients with reduced ejection fraction, which has been shown to improve PAP in this subset of patients.

If symptoms persist (NYHA functional class II–IV) despite maximal medical therapy, surgical intervention is indicated for severe degenerative MR. In asymptomatic severe MR, surgery is indicated when the LV ejection fraction (LVEF) falls below normal (30% to 60%), LV dilation develops, new onset atrial fibrillation appears, or upon development of PH (PASP >50 mm Hg at rest, or PASP >60 mm Hg with exercise). Surgery for chronic severe functional MR with an LVEF <30% should only be considered with refractory severe symptoms (NYHA functional class III–IV) despite optimal medical therapy. The role of MV surgery for functional MR is debated, as the underlying pathology is a poorly functioning dilated LV. In general, repair of the MV is preferred over replacement when valve anatomy is suitable, and should be performed in experienced centers.

Worsening LV function after MV surgery may be due to the increased LV afterload that develops after eliminating the MR, and may necessitate mechanical circulatory support (LVAD). Urgent surgical intervention is the only definitive treatment for acute severe MR, though afterload reduction with nitroprusside or intra-aortic balloon counterpulsation can help stabilize patients until surgery.

Several percutaneous options for MV repair have emerged in recent years. One type of device is implanted in the coronary sinus. The goal of this device is to reshape the contour of the MV annulus and improve leaflet coaptation in functional MR. Several of these devices have shown encouraging results in the proof of concept and feasibility stages, but have failed to translate into reproducible and durable clinical results.

Another percutaneous option is the MitraClip® (Abbott Vascular, Santa Clara, CA), which is commercially available for degenerative (primary) 3 to 4+ MR in patients who are not candidates for surgery. The MitraClip is delivered anterograde across the MV via trans-septal approach to achieve an end-to-end repair of the MV leaflets. The pivotal trial leading to FDA approval of MitraClip was EVEREST II, which randomized patients 2:1 to MitraClip or MV surgery. Patients undergoing MitraClip had an improved safety profile, but less reduction in MR compared to surgery. Clinical outcomes were similar (LV size, NYHA functional class, quality of life measures) between the 2 groups. A large European registry of 628 patients demonstrated similar 1-year mortality rates with both functional and degenerative MR (15.3%), but an increased rate of heart failure admissions with functional MR (25.8% vs 12.0%, \( P_{\text{log-rank}}=0.009 \)). This study also showed a significant reduction in PASP from baseline to discharge and out to 1 year (functional MR: 44.2 mm Hg to 39.2 mm Hg and 40.5 mm Hg, respectively; and degenerative MR: 53.5 mm Hg to 43.4 mm Hg and 42.9 mm Hg, respectively). Matsumoto et al performed serial PASP measurements after MitraClip placement in 48 patients with PH (PASP >50 mm Hg) and 42 patients without PH. Patients with PH had a reduction at 30 days (63.5 ± 9.0 mm Hg to 50.0 ± 13.7 mm Hg), which was sustained at 1 year (50.8 ± 15.3 mm Hg). Preexisting PH was a predictor of 1-year mortality (HR 3.731, 95% CI 1.653 to 8.475, \( P_{\text{=0.002}} \)). A large-scale randomized Phase 3 clinical trial for MitraClip is underway (COAPT, NCT01626079), which includes both functional and degenerative MR.

### Aortic Stenosis

Etiologies of AS include calcification of a trileaflet or bicuspid aortic valve or rheumatic heart disease. The natural history of medically treated symptomatic AS is poor, with a 50% mortality rate over 2 years. Roughly two-thirds of patients with severe AS have concomitant PH. Similar to PH related to

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Degenerative</th>
<th>Functional</th>
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<tbody>
<tr>
<td>Myxomatous degeneration</td>
<td>Repetured chordae</td>
<td>Dilation and/or dysfunction of the left ventricle, causing mitral annular dilation</td>
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<td>Mitral value prolapse</td>
<td>Flail leaflet segment</td>
<td>Poor leaflet displacement</td>
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### Table 1. Mitral Regurgitation Based on Underlying Pathology.

- **Etiology:** Myxomatous degeneration, Mitral value prolapse
- **Degenerative:** Repetured chordae, Flail leaflet segment
- **Functional:** Dilation and/or dysfunction of the left ventricle, causing mitral annular dilation
- **Results:** Increases mortality
- **Pulmonary hypertension in this setting:** In dependent predictor of death over 4 year follow-up period

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[44] MitraClip

[47] MitraClip placement in 48 patients with PH (PASP >50 mm Hg) and 42 patients without PH. Patients with PH had a reduction at 30 days (63.5 ± 9.0 mm Hg to 50.0 ± 13.7 mm Hg), which was sustained at 1 year (50.8 ± 15.3 mm Hg). Preexisting PH was a predictor of 1-year mortality (HR 3.731, 95% CI 1.653 to 8.475, \( P_{\text{=0.002}} \)). A large-scale randomized Phase 3 clinical trial for MitraClip is underway (COAPT, NCT01626079), which includes both functional and degenerative MR.

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MV disease, PH in AS increases mortality regardless of management strategy—medical, surgical, or percutaneous.\textsuperscript{50-52} The degree of PH appears to correlate with left atrial dysfunction and LV diastolic dysfunction.\textsuperscript{14} In addition, those who fail to have improved PAP after intervention have worse mortality and heart failure symptoms.\textsuperscript{54}

Severe AS manifests as angina, heart failure, or syncope. Echocardiography will demonstrate a transaortic pressure gradient of 40 mm Hg (or a transaortic jet velocity of \(>4\) m/sec) and an aortic valve area (AVA) of \(<1\) cm\(^2\) (or an indexed AVA of 0.6 cm\(^2\)/m\(^2\)).\textsuperscript{21,22} Severe AS may be masked by a low CO (so-called "low-flow, low-gradient AS") and should not be overlooked. Intervention (surgical or percutaneous) is indicated with severe symptomatic AS, severe AS with reduced LVEF, or asymptomatic very severe AS (AVA \(<0.7\) cm\(^2\), transaortic jet velocity of \(>5\) m/sec, or transvalvular gradient of \(>60\) mm Hg). Medical management until that point (or in patients deemed unfit for intervention) should focus on guideline-directed treatment of hypertension and hyperlipidemia.

The most common method of assessing operative risk is the Society of Thoracic Surgeons (STS) Predicted Risk of Mortality (PROM), which does not incorporate PH. Alternatively, the European System for Cardiac Operative Risk Evaluation (EuroSCORE) does consider PH in risk calculation.\textsuperscript{53-55} Of note, combined valve disease is not uncommon in this population (namely, concomitant MR). Surgery has long been the standard of care for those requiring aortic valve replacement (AVR), as valve repair for AS is feasible. Transcatheter aortic valve replacement (TAVR) has now emerged as a commercially available option worldwide for patients who are considered at prohibitive or high risk for surgical AVR. The 2 most widely used valves are the Edwards Sapien XT and S3 valves (balloon expandable) and the Medtronic CoreValve and Evolut R valves (self-expanding).\textsuperscript{56-58} There are ongoing trials that aim to expand the indications for TAVR to include those at moderate risk. Surgical AVR and TAVR have been identified as treatments for PH caused by LV outflow obstruction secondary to AS, both demonstrating a significant and durable reduction in PAP out to 1 year.\textsuperscript{11,59} The presence of new or worse PH post TAVR has been shown to increase mortality, a phenomenon that is most often related to perivalvular regurgitation.\textsuperscript{60} Our data have shown the importance of defining preprocedure PH in this population in order to tailor periprocedure medication and fluid management. Also, patients with a precapillary component can be expected to have less improvement in post-TAVR PH.\textsuperscript{59}

**Aortic Regurgitation**

Both aortic root and primary aortic valve abnormalities can result in aortic regurgitation (AR). Leaflet failure or perivalvular regurgitation of bioprosthetic aortic valves can result in AR as well. Chronic AR can be present for many years without symptoms or LV compromise, with the LV increasing total stroke volume to maintain normal CO. Eventually left atrial pressure increases, causing symptoms, and systolic dysfunction will develop, as compensatory LV hypertrophy is insufficient. As a result, pulmonary venous pressures will rise, causing PH (defined as PASP \(>60\) mm Hg) in 24% of patients in a case series of 139 patients with severe chronic AR.\textsuperscript{21,62} While mild or moderate AR carries a good prognosis, severe AR will result in symptoms or LV dysfunction at a rate of 4.3% per year.\textsuperscript{21} Echocardiography remains the central tool for evaluation, which, in addition to PAP estimation, provides quantitative assessment such as regurgitation volume, regurgitant fraction, and effective regurgitant orifice area.\textsuperscript{61} When echocardiography is suboptimal, magnetic resonance imaging (MRI) can be considered.

Vasodilators (nifedipine, ACE) are the primary medical intervention for patients with AR and diastolic hypertension, while beta blockade should be avoided.\textsuperscript{21} The benefit of vasodilators in asymptomatic patients with severe AR is not clear.\textsuperscript{62,63} Central to the management of AR is root or valve intervention prior to development of irreversible LV dysfunction. Aortic valve replacement in chronic AR has been shown to effectively reduce PVR (4.7 \(\pm\) 3.5 to 1.5 \(\pm\) 0.8 Wood units) and normalize PASP in a series of 139 patients from Naidoo et al.\textsuperscript{60} While chronic AR can be monitored until symptoms or LV dysfunction develop, acute severe AR requires emergent surgical intervention.

**CONCLUSION**

With an aging population, VHD and WHO 2 PH are increasingly prevalent and warrant an experienced team in addressing the specifics of intervention. This patient population carries a higher procedural risk, but intervention is the only chance for improvement. Our data show the feasibility and importance of approaching this cohort with a multidisciplinary team pre- and postintervention. One should identify those patients that need targeted pulmonary vasodilators, either due to existence of precapillary PH from systemic scleroderma or lung disease, or due to the more severe CfpPH. Postprocedural management of PH must be guided by defining components of prior interventions.

**References**


Cardiac magnetic resonance imaging (CMR) provides an important and complementary role to conventional imaging in the evaluation of patients with pulmonary hypertension (PH). Echo-cardiography remains vital given its ability to quickly assess cardiac morphology, function, and hemodynamics. It is also portable, readily available, and relatively inexpensive. However, certain limitations of echocardiography do occur in PH patients such as inability to fully or accurately characterize the right ventricle (RV), which remains crucial for therapeutic decision making and prognostic determination. Given the geometric complexity of the RV as well as patient-specific factors such as obesity, echocardiography may fail to adequately depict the RV. Conversely, CMR is well suited for PH imaging for various reasons, not least of which is its ability to fully characterize RV morphology and function. In addition, CMR provides various components during a PH examination, including assessment of pulmonary artery (PA) flow and stiffness, ventricular function and strain, shunt, emboli, and tissue characterization.

Generally, echocardiography provides a detailed and accurate assessment of the RV in many PH patients. However, in those instances where accuracy or visualization is limited, or where more precise determination is required, CMR should be strongly considered as it remains the reference standard for RV assessment. On a typical CMR examination, a series or stack of short- and long-axis cine images are performed and post-processed using commercially available software. Left and right ventricles are traced from systolic and diastolic still frames providing volumetric data, allowing for calculations of end-diastolic and systolic volumes, ejection fraction, mass, and stroke volume. As the severity of PH progresses, the RV thickens, enlarges (Figure 1), and will subsequently fail demonstrated by a progressive decline in ejection fraction. These changes to RV size and function are tightly coupled with mortality. Also, as pulmonary pressures rise, there is a characteristic flattening of the interventricular septum leftward. The degree of flattening can be quantified by comparing the curvatures of the interventricular septum to left ventricular free wall, a value that is strongly correlated to the degree of PH. Evaluation of myocardial strain using conventional tagging or other novel sequences may also accurately characterize the RV, but at this point is largely relegated to research protocols.

The ability to accurately assess PA stiffness presents an exciting new avenue for CMR. The development of adverse pulmonary vascular remodeling is the hallmark feature, which begins the cascade of pulmonary arterial hypertension (PAH). With the use of specific flow sequences, CMR can accurately measure cross-sectional phasic changes to the PA, thereby providing a means...
Figure 1: Four-chamber long axis cine images. A) Normal RV, normal curvature of the interventricular septum (arrows). B) Significant RV dilation and hypertrophy as seen in severe PH. The curvature of the interventricular septum is lost (arrows) and presents as a “D”-shaped left ventricle. Also notice the presence of pericardial effusion and dilated right atrium: both are markers of poor prognosis in PH.

Figure 2: Short axis flow images of the pulmonary artery and aorta in normal, mild, and severe PH.
to calculate indices of PA stiffness including pulsatility [(PA area_{max} – PA area_{min})/PA area_{min}] (Figure 2). As PH progresses, the PA typically dilates and the degree of pulsatility declines, reflecting loss of elasticity and worsening stiffness.6,7 This technique may provide a means to detect pulmonary vascular remodeling at an earlier stage of development, and may also ultimately be considered a target for PH-specific therapies. One potential role of CMR is detection in those patients who are “at risk” (i.e., scleroderma patients) or have clinical findings suggestive of early pulmonary vascular remodeling, but exhibit negligible pulmonary pressure elevations above normal during right heart catheterization. Pulmonary arterial measurements from CMR can also be coupled with invasive catheterization, yielding additional characterization of compliance, capacitance, and distensibility and may hold promise in assessing ventricular-vascular coupling.8,9

The use of magnetic resonance angiography (MRA) or pulmonary perfusion to assess for World Health Organization Group 4 chronic thromboembolic PH (CTEPH) and pulmonary blood flow is also a part of routine PH CMR protocols. While lacking the sensitivity of traditional testing such as ventilation perfusion lung scans or computed tomography angiography, MRA may be useful in selected cases to aid in the diagnosis. In addition to CTEPH, conventional cine and flow sequences may also identify other potential causes for PH that may not have been previously recognized such as atrial septal defects and shunts, patent ductus arteriosus, and anomalous pulmonary veins. Following perfusion imaging, delayed imaging post-contrast is performed to assess whether late gadolinium enhancement is present in the myocardium, a finding suggestive of cardiac pathology such as with fibrosis, scar, infarction, or infiltrative cardiomyopathy. In the case of PAH, late gadolinium enhancement is often pictured in the RV insertion sites, which is a finding suggestive of increased wall tension and strain. An appearance of scar in the interventricular septum RV insertion sites may reflect worsened PH and may be linked to poor prognosis.10

While it is highly unlikely that CMR would replace conventional echocardiography or right heart catheterization, there is little doubt regarding its value in selected patients with PH where the diagnosis or cause remains unclear or the RV is poorly characterized. Newer techniques and data will be necessary to determine the usefulness of other sequences that measure such things such as myocardial strain, pulmonary vascular remodeling, and tissue characterization. Certainly, CMR is not without its limitations such as cost, limited availability, expertise, and study time. Patient-related limitations include claustrophobia and potential contrast reactions. However, the superb tissue characterization combined with important morphologic and physiologic data afforded by CMR make it an extremely useful and promising means for assessment of pertinent changes to the pulmonary circulation and RV in the setting of PH. No other technique at present provides such a comprehensive means of assessment of important morphologic changes to the heart and vasculature in this patient population. While we cannot definitively state whether CMR is presently underutilized in PH, its value and appreciation coupled with new advancements and research will likely increase the proportion of CMR used in PH in the future.

References
PULMONARY HYPERTENSION ROUNDTABLE

Pulmonary Hypertension Due to Left Heart Disease

Guest editor Teresa De Marco, MD, along with Brian Shapiro, MD, Mayo Clinic, Jacksonville, FL, convened a panel of experts to discuss the challenges in diagnosis and treatment and the emerging science regarding pulmonary hypertension due to left heart disease. Contributing to the engaging discussion were James Fang, MD, University of Utah School of Medicine; Barry Borlaug, MD, Mayo Clinic, Rochester, MN; and Srinivas Murali, MD, Allegheny Health Network, Pittsburgh, PA.

Dr De Marco: Thank you for joining Dr Shapiro and me for a roundtable discussion to explore salient topics in pulmonary hypertension (PH) due to left heart disease. As experienced thought leaders, your perspective on the major issues and challenges we face in dealing with this entity will be valuable to our readers. In recent years, there have been multiple review publications on the topic. Recently, the Fifth World Symposium Task Force on PH and Left Heart Disease published a proposal for the hemodynamic definition, classification, and nomenclature for PH and left heart disease. I would like to start the discussion with you, Dr Fang, as you were the primary author for a summary statement on the topic published in the Journal of Heart and Lung Transplantation. What are your thoughts on the diastolic pulmonary gradient, the transpulmonary gradient, and pulmonary vascular resistance (PVR) in the definition for PH in left heart disease? Which hemodynamic parameter or parameters would you advocate utilizing in the hemodynamic definition and why?

Dr Fang: Thank you, Dr De Marco; that's a great question. We traditionally often have used things like transpulmonary gradient and PVR, despite all their limitations, because of the nature of the methods in clinical practice of collecting those data. The issue of the diastolic gradient is an interesting one. The evidence to date has been somewhat controversial. There are studies that suggest that the diastolic gradient is a reflection of pulmonary vascular disease. And other studies have not been able to find that that correlates adequately with outcomes. In terms of the best measurement to make, I still think that our traditional ways of doing it are what we have the largest evidence base for. This idea of mixed PH is an important issue to sort out, because we really don’t understand why people get mixed PH. That being said, I think work by Barry Borlaug and others, looking at compliance of the vascular bed, may in fact be a much stronger and better determinant of right ventricular (RV) vascular coupling as we look into the future. And I do think that these measurements can be made clinically and then integrated into the routine evaluation of patients with secondary PH.

Dr De Marco: Would you like to provide your perspective, Barry?

Dr Borlaug: Yes, I agree with everything Jim is saying. After the initial sort of embrace of the diastolic pressure gradient (DPG) as the way to go, there have been a number of studies in heart failure patients really questioning how useful it is. And we’ve looked at this. We published a paper a couple of years ago looking at different ways to define pulmonary vascular disease and left heart failure. And at that time, DPG wasn’t really out there, so we didn’t even include it, but it really didn’t predict outcome. Whereas, as Jim mentioned, things like pulmonary artery (PA) compliance were the most robust. Which makes sense, because PA compliance starts to fall off, even when the PVR abnormalities are pretty minor, because of the hyperbolic relationship between resistance and compliance. So I think that compliance is probably going to be a better way to do it. And whether that is from problems with the DPG itself or whether that’s just more logistical issues with getting a good DPG in terms of where you’re assessing diastolic pressure and wedge pressure in the respiratory cycle, whip or ringing artifact on the catheters, these are important sort of devil-in-the-detail issues that probably contribute to why it’s not a real good predictor. So, I’m not enthusiastic about using DPG to define pulmonary vascular disease in patients with heart failure.

Dr De Marco: Agreed. More and more data are coming forth that, in fact, the diastolic pulmonary gradient is not related to outcome. Although it makes pathophysiologic sense, since the diastolic pulmonary pressure and, hence, the diastolic pulmonary gradient is independent of stroke volume, reflecting abnormalities of the pulmonary vasculature itself not driven by cardiac output. However, it is ventricular function and cardiac output that is tied to prognosis; therefore, the pulmonary artery systolic pressure and the transpulmonary gradient, which are dependent on stroke volume, may be more predictive of outcomes as is the PVR, which takes into account the cardiac output reflective of ventricular function in the calculation.

So, Dr Murali, why is the presence of PH in the setting of left heart disease important in clinical practice?

Dr Murali: Pulmonary hypertension, when it coexists with left heart disease, irrespective of the particular kind of left heart disease—whether it is a muscle disease or if it’s a valve disease—is associated with a significantly higher morbidity and mortality. As we continue to find novel ways to improve morbidity and mortality in left heart disease, we have to tackle the man-
Dr De Marco: Thank you. So Brian, would you like to take it from here?

Dr Shapiro: You got it. So this one’s to Dr Borlaug. And the question is, how does one differentiate those patients with Group 1 pulmonary arterial hypertension (PAH) from those patients with PH with left heart disease secondary to heart failure with preserved ejection fraction (HFpEF), based clinically, on symptoms and signs, as well as echocardiography.

Dr Borlaug: The only way to really do it definitely obviously is with a catheter, because it’s a hemodynamic definition, based on the presence or absence of high left heart filling pressures. But you can probably get a very good sense clinically, as you suggest, Brian. The things you would look for would be typical risk factors that would be associated with Group 2 HFpEF-related PH, which would be older people, so probably above 65, at least 60, with common comorbidities that we see in HFpEF, like systemic hypertension, which is in the vast majority, along with other things like diabetes or metabolic syndrome, obesity, female sex, though of course many women also have Group 1 PH, so the discrimination there probably isn’t as good. In terms of ventricular function in echocardiography, typical things that we’d see in patients with HFpEF-related PH would be left atrial enlargement, concentric ventricular remodeling or hypertrophy, though that’s not necessary, of course—and echo Doppler estimates indicative of high left heart filling pressures, though again those are very imperfect measures. In studies that have looked at this, they don’t seem to discriminate real well. But those are the things that I would look for ahead of time. And in people where you really can’t tell, obviously you need to do a hemodynamic assessment.

Dr Shapiro: Yes.

Dr De Marco: I have a question for you, Barry. What’s the value of assessing “notching” of the Doppler signal in the right ventricular outflow tract? What about other novel parameters? Is there a role for that or are they too difficult to ascertain on a regular echo?

Dr Borlaug: That’s a great, great point, Teresa. You know, Paul Forfia’s group has published a number of papers on this. I think in the right hands, in groups that have a lot of expertise, it seems to be a pretty good indicator. People with a lot of pulmonary vascular disease get this big reflected wave, which decelerates flow or causes this notch. In our hands, we don’t tend to see it quite as often, but I can tell you sort of anecdotally. I haven’t looked at it really systematically in our reports, but I think the people that we do tend to see it in more are the people with really more advanced Group 1 PH or maybe chronic thromboembolic PH. We don’t tend to see it as often in patients with left heart disease-related PH. Whether that’s just that they don’t have such profound pulmonary vascular disease or not, I don’t know. I think if you see it, that’s very useful. I think if you don’t see it, the question then is: is it an issue with the quality of the echo or the severity of the pulmonary vascular disease, or something else?

Dr De Marco: And do you differentiate between a midsystolic notch versus a late systolic notch? Have you found that useful in clinical practice?

Dr Borlaug: I have not. In my practice, which is mostly heart failure patients, not non-heart failure-related PH, I have not found it to be a very helpful thing to look for.

Dr Shapiro: So Barry, if there are one or two things that you would look for on the echo that would help convince you more it was HFpEF, what would you say would be your most reliable findings?

Dr Borlaug: I think the presence of left atrial enlargement would be very helpful. I think that if there is profound diastolic dysfunction, that would be helpful. So if the ratio of transmitral flow to tissue Doppler early diastolic velocity, or the so-called E/E prime ratio, is really high—greater than 15 or 20—that would be helpful. If there is really profound abnormal mitral filling pattern, you know, a restrictive or at least Group 2 type pattern there, I think those would also be helpful. The old thinking used to be that you almost had to have concentric hypertrophy or at least concentric remodeling, which we would define by an increase in wall thickness relative to end diastolic dimension. We see a lot of people these days with HFpEF that have normal geometry. So I’m not sure that that is as useful as we used to think it was. I think the indicators of either high left heart filling pressures at the time of the study, namely the Doppler and tissue Doppler parameters, and then the markers of more chronic, sustained elevation of left heart pressures, like left atrial enlargement, would probably be the most useful.

Dr Shapiro: I know a lot of programs are also starting to do these exercise echo hemodynamics, where you get exercise pulmonary pressures and exercise E/E prime, suggestive of increased filling pressures. Would you trust those or do you rely on those, or how do you find those fit in your clinical practice?

Dr Borlaug: I don’t trust them a great deal. I mean, the Pearson R value for E/E prime versus directly measured wedge pressure usually runs in the range of 0.4 to 0.5. So there’s a lot of scatter. We’ve looked at this. We have unpublished data from a very large population of patients that had simultaneous assessments. And they’re definitely correlated with one another, but not really strong. In particular, the change in E to E prime is not a very robust indicator of the change in wedge pressure. So what we typically see, for example, in HFpEF or heart failure with reduced ejection fraction (HFrEF) patients is the wedge pressures going from maybe 17 to 35. And the E/E prime is maybe going from 14 to 15 or something like that. So there’s not this nice linear relationship between the two. And I don’t have a lot of confidence in that personally. There’s a number of studies now. I think one in Circulation Heart Failure recently sup-
ports the problems with E/E prime exercise as an indicator. The PA systolic pressure, if you can get a good Doppler envelope, I think is good. An old study from years back indicated that when they did it with agitative saline, that does appear to help and gets you a little bit better signal, but it makes it a little bit more of a pain to do. In our study, again this is unpublished, we were able to get a PA systolic pressure estimate during exercise about 50% of the time. So not great, but we got one about 50% of the time. And in that case, we saw a very good correlation with invasively measured PA pressures. The correlation weakens with exercise because your PA pressure estimate obviously is based on the tricuspid regurgitation (TR) velocity, which is telling you the gradient between the RV and the right atrium (RA). We often make this assumption that the RA pressure is just 5 or 10 in everybody. But in reality, in heart failure patients with exercise, we see RA pressures that vary from 0 to 50 or 60 mm Hg. So during the exercise, we can substantially underestimate the true PA systolic pressure, even if you’re able to get a good envelope. Now, if the velocity is high, at least you know that it’s probably very significant. You just have to keep in mind that you might be underestimating it. And if you don’t have a good signal, you’re still kind of left wondering.

**Dr Borlaug:** One more point I would make on that. And I don’t mean to come out anti-echo. It’s certainly a very useful test. But as a person whose practice is largely doing invasive exercise tests, a lot of the referrals I get are people that already had a noninvasive and sort of echo exercise test that ended up being kind of abnormal or equivocal. And then you just sort of wonder, how often they should have just been referred directly to the cath lab in the first place to save a little bit of money. Of course, it’s a referral population, so that might be a little biased.

**Dr Shapiro:** I tend to agree with you on the exercise echoes. Interpreting the E or the TR envelope can be so difficult, particularly with the scatter that you get on the TR signal and so forth, that can make it very difficult to get an accurate measurement.

**Dr Murali:** I agree with both your comments on that. You know, I think when you ask the question, what is the best way to recognize early PH related to left heart disease in a community setting, I think an exercise echo would not be the test of choice.

**Dr De Marco:** So with that regard, how would you differentiate PAH from PH with left heart disease in the setting of HFpEF based on invasive hemodynamics? Do you have a set invasive protocol, Srinivas, that you can recommend to us?

**Dr Murali:** Well, again, I think unfortunately, this is one of the gaps in our knowledge at this point in time. Clearly, there is a dire need to have a standardized protocol in making this assessment, and different institutions and different investigators have adopted protocols that they find and that they feel is most appropriate. In our institution, we do have an exercise hemodynamic laboratory, where we are able to do supine bicycle exercise, with the catheters placed in the neck. And we typically follow a ramp protocol, increasing workload by 10 every minute. We certainly measure PA pressures and around the time the patient gets to peak exercise, we would quickly measure the wedge pressures, as well, and do a mixed venous oxygen saturation and do thermodilution cardiac outputs at that setting. We are not equipped in our laboratory to measure oxygen consumption simultaneously, which some laboratories are able to do a VO2 assessment, as well, which I think is extremely useful.

**Dr De Marco:** What do you do, Barry?

**Dr Borlaug:** So we do both supine and upright exercise. We tend to do more supine because it’s just easier, it’s more feasible. It’s a little trickier to get catheters in, have everything zeroed at the phlebotastic access and then get them back up again, especially in older people, and get them onto the upright bike. But we can certainly do both. So what we’ll do is get access in the radial artery and in the jugular. We’ll put a 9-French sheath in the neck, so we can measure the right atrial pressure throughout the case. And I think that’s very important, as well. Then we put a balloon wedge catheter to get samples and high fidelity pressure data at rest and during exercise. We do expired gas analysis during the test and, you know, there is a bit more expense there. There is a bit more training. There is calibration needed on a daily basis. But we find it to be extremely useful, because I think most people would agree that direct Fick outputs to measure cardiac output at rest and exercise would be considered the gold standard. If you look at how much the oxygen consumption goes up during exercise, you can accurately say whether the cardiac output reserve was appropriate or not. That’s because it’s well known in humans that for every 1 mL increase in oxygen consumption, there should be a 6 mL increase in cardiac output, if the heart is doing its job, to meet the body’s metabolic needs. So in these PAH patients, we can see if they have high filling pressures obviously, but this really gives us a good sense for the adequacy of their cardiac output reserve, which is very often abnormal in patients with PH and left heart disease. Having the right heart pressures, their RA pressure and the wedge pressure or the PA pressure together is useful, because sometimes you see these people where the 2 go up in tandem and they almost equalize. And while not well-studied, that suggests that those people are having more pericardial restraint and they might have a somewhat different kind of disease compared to somebody whose wedge pressure goes up to 35 but their RA pressure stays at 10. So again, that’s not well-studied, but we think that that’s probably useful to understand that.

**Dr Shapiro:** What do you do for volume loading and things of that nature in the cath lab or how often does one have to perform that?

**Dr Borlaug:** We do volume loading. We published a paper earlier in 2015 where we compared volume loading and exercise in the same patients. They did
exercise first; everything came back to recovery. And then they got a very aggressive volume load, 10 cc/kg, wide open, over 5 minutes. So it’s about 150 cc a minute, prewarmed so we don’t drop their core temperature. And we see that filling pressures go up. But the increase in heart failure patients with saline is not nearly what we see with exercise. And, in fact, it’s not statistically different from what we see in normal people, in whom also it’s not uncommon to have an increase in wedge pressure above 15. So the saline loading, it’s better than nothing, but it’s not as sensitive or specific as exercise. Another group from Vanderbilt published a paper where their practice has just been to give 500 cc much slower, I think over 10 minutes, and they do see a number of people that had an elevation in wedge pressure above 15 mL. Again, as I mentioned, we do see this not uncommonly in some of the normal people, maybe 20% of the time. So I think that there are some issues there with the specificity of that finding.

Dr Shapiro: I would have to believe that nationally and internationally, you know, the rate of a program having the ability to exercise, do exercise-invasive hemodynamics must be low. There may be a number out there, I don’t know, but I would expect it to be low. But for those programs or those practices out in the community that, you know, want to make this diagnosis invasively, but only have the ability to do baseline-type hemodynamics, is that accurate? Is that a good way to go? Or what could they be doing to enhance that?

Dr Borlaug: Well, I think saline is better than nothing. I mean, any sort of provocative maneuver, any sort of stress, is going to help to bring out abnormalities. So I still think there’s value to doing it. I think that if the wedge pressure goes above—probably above 18 with the saline load—that would be pretty good evidence that they probably do have significant left ventricular (LV) diastolic dysfunction. It’s just not quite as good as what we see with exercise.

Dr Borlaug: But it’s better than nothing.

Dr Shapiro: How about simple weights, if they wanted to do curls or whatever kind of exercise in the cath lab; would that be helpful?

Dr Borlaug: You can do it. The problem is, a lot of people when they do sort of these butterflying or whatever type of weightlifting that is, they involuntarily do a Valsalva maneuver, which then increases intrathoracic pressure. So then basically all pressures are going up, even in the absence of a true change in distending intracardiac pressures. So you can get this false-positive because they’re sort of bearing down as they’re doing the lift.

Dr De Marco: And what agents do you use in the various scenarios? For example, with WHO Group 1 or WHO Group 2?

Dr Murali: Our institution uses inhaled nitric oxide. So our protocol goes from 10 parts per million, all the way to 40 parts per million, for both scenarios, for both groups.

Dr De Marco: Even for patients with PAH and left heart disease? Have you run into elevations in wedges and pulmonary edema in the WHO Group 2?

Dr Murali: We haven’t quite gotten into pulmonary edema, but we have seen elevations in wedge pressure in WHO Group 2 patients. So that’s one of the things to keep in mind when you test them. But it is quite valuable. The other agent—which is not an acute vasoreactivity testing agent—we have used in some patients—especially if their cardiac indices are low, is to start them on milrinone infusion and then bring them back to the cath lab after a few days of milrinone therapy to see if the numbers have improved.

Dr De Marco: And Jim, what do you do in these scenarios for WHO Group 2? What’s your protocol?

Dr Fang: We do also use inhaled nitric oxide. Probably most commonly, we use Nipride, if the systemic vascular resistance (SVR) is elevated. And we titrate the Nipride to potentially hypotension or just short of that. We do know patients who get very hypotensive from Nipride from the old Stanford experience don’t do well. Secondly, if the SVR is low and
the PVR is high, we will sometimes just try nitrates. And then, like Srinivas, we also are a big fan of using milrinone. We use the protocol of the bolus of milrinone, 50 mcs per kilo over a minute or two. You see the peak effect somewhere between 5 and 15 minutes. This primarily lowers the PVR by increasing the output, at least from the calculated point of view.

**Dr De Marco:** And for both of you, what do you feel are the important considerations relevant to PAH and left heart disease, in the context of heart transplantation and left ventricular assist device (LVAD) implantation? So you want to start, Srinivas?

**Dr Murali:** I think transplantation criteria are a little bit stricter. We would, in our program, have certainly wanted to see the transpulmonary gradient be less than 12 and the pulmonary vascular distance to be as close to 3 Wood units as possible before they are listed for transplantation. As far as LVAD is concerned, it’s a slightly different approach. I think that we have generally not excluded patients for consideration for LVAD implantation on the basis of transpulmonary gradient and/or PVR. It’s been our experience that in many of those patients with the currently used LVADs in clinical practice, both the HeartMate II axial flow pump, as well as the HVAD centrifugal pump, we have been able to unload the left ventricle with improvements in hemodynamics, as it relates to pulmonary pressures, transpulmonary gradient, and PVR over a variable period of time. So for transplant, we want to see the numbers come down before re-enlisting them. But for LVADs, we would proceed with the LVAD, as long as we feel comfortable with respect to the risk of right heart failure postoperatively and then follow their hemodynamics on LVAD and wait until they improve to the levels I alluded to before listing for transplant.

**Dr De Marco:** I agree. In fact, we’re using VADs at our institution, again provided the RV function is in a reasonable range, as a bridge to transplant. And over time, the PVR markedly improves in virtually all of these patients and then they do become transplant candidates. And oftentimes, we may, in addition, add phosphodiesterase inhibitors to those patients where we haven’t attained a PVR that would allow them to go to transplant. So these are 2 strategies that we’ve employed. What about you, Jim?

**Dr Fang:** Well, I would concur and echo everything that both you and Srinivas have said. From a pathophysiologic standpoint, I think a great example of how they’re really 2 components physiologically to the elevation in PVR and the PH: one, of course, is a dynamic component that we tend to try to affect acutely with vasodilators, diuretics, etc. And, of course, there is the more anatomic part of the equation that obviously requires a, for lack of a better word (laughs), putting down the rage of activation, so you can get the positive remodeling that you want to see in the pulmonary circulation. And I think the VADs help to provide that.

**Dr Shapiro:** Absolutely. I think, Barry, we were going to switch gears a little bit to treatments. In terms of the comorbidities, what are the most important comorbidities that one looks for in a typical patient with HFpEF, PH with left heart disease? And, in our experience, what are the ones that are most successfully treated and make a difference in a positive outcome?

**Dr Borlaug:** Well, I’m afraid I don’t have real good experience versus real positive outcomes. It’s such a challenging disease. I mean, I think that the people with PH and HFpEF in general are just the people with more advanced HFpEF. So there are some people that have high filling pressures and PH that’s just restricted to exercise. These people are profoundly limited. They have very bad, lifestyle-limiting symptoms. I mean, many of them are crying literally in the office. They are miserable. But they’re not getting admitted for pulmonary edema or peripheral edema; they’re not going into the hospital. It’s more lifestyle changes. The people with more advanced disease who have high filling pressures at rest, these are the people that tend to have more PH. And we’ve started to look at what distinguishes these people. It’s probably more prolonged heart failure, more comorbidities, so they tend to have more hypertension, more diabetes and metabolic syndrome, greater age, and worse kidney function, which is probably not surprising. When the kidneys are not able to excrete the solute anymore, that seems to accelerate the progression. You know, in terms of managing the comorbidities, we often look at good blood pressure control, weight loss, treating sleep apnea: of course you’re going to do all this. The evidence that that is going to lead to clinically meaningful improvements in their heart failure is slim and none. We do have some data now on single-center retrospective data from Mayo that we published last year, looking at coronary disease as a comorbidity in HFpEF, regardless of the presence or absence of PAH. And the patients with coronary disease have worse outcomes. And revascularization was associated with better outcomes. We don’t know what’s doing in terms of the hemodynamics and the filling pressures and the pulmonary artery pressures, but that’s one comorbidity that in these, at least in HFpEF patients with PAH, I have a very low threshold to look for.

**Dr Shapiro:** So provided that all the comorbidities are being addressed and you’ve got a patient who is in your office with severe HFpEF and secondary PAH, what are your favorite go-to both pharmacologic and nonpharmacologic treatments that have been most successful for you?

**Dr Borlaug:** We said for years that there’s “no evidence for diuretics in heart failure.” But, of course, we’ve always known that’s not the case. And now with the evidence from the Champion study of the PA pressure sensor device, we know that when you manage people with heart failure based on their hemodynamics and modify their diuretics, that you can reduce hospitalizations. And that’s been shown even stronger in HFpEF, in another analysis from that.
trial. So yeah, good old loop diuretics I think are the only thing that I’m convinced really works. People talk about nitrates. We will have data on that soon. There was a large, or pretty good-sized, phase 2 trial of isosorbide mononitrate, which has now been completed and will be reported in HFpEF. We know from the RELAX trial that PDE-5 inhibitors were not effective, though there was a small single-center study that showed benefits in a very atypical HFpEF population that had much more advanced PH. Beta-blockers, not good evidence. Same thing with calcium channel blockers. And then other people are using off-label things, like ranolazine and such, but there’s really no good data to support any of those. So, for me, it’s diuretics. I look forward to what the others think.

Dr De Marco: Okay. I have one final question for Jim. From your perspective, what are the most important diagnostic and treatment gaps that remain in the knowledge base for PAH due to left heart disease? And what does the future hold?

Dr Fang: Well, great question. I think one of the basic knowledge gaps that is still one of the elephants in the room is whether or not it’s a disease marker or a risk factor. It does fall out often in multivariate analyses as an independent predictor, which would suggest that it’s a factor. But one of the unexplored areas is how much of that is really just a surrogate for time. Time in most heart failure studies is poorly controlled for, primarily because the onset of the disease is very difficult to quantify or to have any precision about. If we think about the pathophysiology of PH, clearly the upregulation of growth factors and other factors, like endothelium that lead to pulmonary vascular remodeling, are time-dependent issues. So I think that still remains a very important issue that really outlines a whole field. Because, in fact, if it’s simply a risk marker, then we need to be a little bit more proximal in our targeting of PH. Number 2 is that if we agree that it’s a separate issue unto itself and not simply an unrecognized surrogate of something else, the issue is to find drugs that are selective for the pulmonary bed or methods of delivery that are selective for the pulmonary bed. One of the things that complicate the treatment of pulmonary vascular disease, of course, is trying to find specificity for that organ bed without producing systemic and off-target effects. So that’s sort of very brief, but I think the two most important issues.

Dr Shapiro: On behalf of Dr De Marco and myself, I really want to thank Drs Fang, Murali, and Borlaug for this excellent discussion on PH and left heart disease. I am confident that your insights will be a huge asset to those who care for patients with this common disease. And once again, I want to thank you so much for your help.

Dr De Marco: Thank you, everyone.
For the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability.

**WANT TO IMPROVE YOUR PAH PATIENTS’ EXERCISE ABILITY? TYVASO MAY HELP.**

Consider adding Tyvaso, an inhaled prostacyclin analogue, studied solely as add-on to oral background monotherapy (sildenafil or bosentan)

**Tyvaso improved 6MWD at week 12**

<table>
<thead>
<tr>
<th>Background therapy</th>
<th>Tyvaso improved 6MWD at week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 m peak*</td>
<td>median improvement in 6MWD with Tyvaso at week 12 (P&lt;0.001)</td>
</tr>
<tr>
<td>14 m trough*</td>
<td>median improvement in 6MWD with Tyvaso at week 12</td>
</tr>
</tbody>
</table>

**INDICATION**

Tyvaso is a prostacyclin vasodilator 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 III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

**IMPORTANT SAFETY INFORMATION FOR TYVASO**

- Tyvaso is intended for oral inhalation only. Tyvaso is approved for use only with the Tyvaso Inhalation System
- The safety and efficacy of Tyvaso have not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease) and in patients under 18 years of age. Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect
- Tyvaso may increase the risk of bleeding, particularly in patients receiving anticoagulants
- In patients with low systemic arterial pressure, Tyvaso may cause symptomatic hypotension. The concomitant use of Tyvaso with diuretics, antihypertensives, or other vasodilators may increase the risk of symptomatic hypotension
- Hepatic or renal insufficiency may increase exposure to Tyvaso and decrease tolerability. Tyvaso dosage adjustments may be necessary if inhibitors of CYP2C8, such as gemfibrozil, or inducers of CYP2C8, such as rifampin, are added or withdrawn
- There are no adequate and well-controlled studies with Tyvaso in pregnant women. It is not known whether treprostinil is excreted in human milk
- The most common adverse events seen with Tyvaso in ≥24% of PAH patients and more than 3% greater than placebo in the placebo-controlled clinical study were cough (54% vs 29%), headache (41% vs 23%), throat irritation/pharyngolaryngeal pain (25% vs 14%), nausea (19% vs 11%), flushing (15% vs <1%), and syncope (6% vs <1%)


Please see brief summary of Full Prescribing Information on following page. For more information, please see Full Prescribing Information, Patient Package Insert, and Tyvaso Inhalation System Instructions for Use manual. These items are available at www.tyvaso.com.

For additional information about Tyvaso, visit www.tyvaso.com or call 1-877-UNITHER (1-877-864-8437).
**INDICATIONS AND USAGE**

TYVASO® (treprostinil) Inhalation Solution is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). The effects diminish over the minimum recommended dosing interval of 4 hours, treatment timing can be adjusted for planned activities. While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

Patients with Pulmonary Disease or Pulmonary Infections—The safety and efficacy of TYVASO have not been established in patients with significant underlying lung disease (e.g., asthma or chronic obstructive pulmonary disease). Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect. Risk of Symptomatic Hypotension—Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with TYVASO may produce symptomatic hypotension.

Patients with Hepatic or Renal Insufficiency—Titrate slowly in patients with hepatic or renal insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal function.

Risk of Bleeding—Since TYVASO inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulant therapy.

Effect of Other Drugs on Tyvaso—Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both Cmax and AUC) to treprostinil. Co-administration of a CYP2C9 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness.

**ADVERSE REACTIONS**

The following potential adverse reactions are described in Warnings and Precautions:

- Decrease in systemic blood pressure
- Bleeding

Adverse Reactions Identified in Clinical Trials—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. In a 12-week placebo-controlled study (ERUPTRA™) of 235 patients with PAH (WHO Group I) and nearly all NYHA Functional Class III, the most commonly reported adverse reactions in TYVASO included: cough and throat irritation; headache, gastrointestinal effects, muscle, jaw or bone pain, flushing and syncope. Table 1 lists the adverse reactions that occurred at a rate of at least 4% and were more frequent in patients treated with TYVASO than with placebo.

**TABLE 1: ADVERSE EVENTS IN >2% OF PAH PATIENTS RECEIVING TYVASO AND MORE FREQUENT THAN PLACEBO**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>TYVASO n=115</th>
<th>Placebo n=120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>62 (54)</td>
<td>35 (29)</td>
</tr>
<tr>
<td>Headache</td>
<td>47 (41)</td>
<td>27 (23)</td>
</tr>
<tr>
<td>Throat Irritation/Pharyngitis</td>
<td>29 (25)</td>
<td>17 (14)</td>
</tr>
<tr>
<td>Syncope</td>
<td>22 (19)</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (15)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Flushing</td>
<td>7 (6)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

*More than 3% greater than placebo

The safety of TYVASO was also studied in a long-term, open-label extension study in which 206 patients were dosed for a mean duration of 2.3 years with a maximum exposure of 5.4 years. Eighty-nine (89%) percent of patients achieved the target dose of nine breaths, four times daily. Forty-two (42%) percent achieved a dose of 12 breaths four times daily. The adverse events during this chronic dosing study were qualitatively similar to those observed in the 12-week double-blind placebo controlled trial. Adverse Events Associated with Route of Administration—Adverse events in the treated group during the double-blind and open-label phase reflecting irritation to the respiratory tract included: cough, throat irritation, pharyngitis, pain, epistaxis, hemoptysis and wheezing. Serious adverse events during the open-label portion of the study included pneumonia in 15 subjects. There were three serious episodes of hemoptysis (one fatal) noted during the open-label experience.

**DRUG INTERACTIONS**

Drug interactions with TYVASO have been conducted with orally (treprostinil diolamine) and subcutaneously administered treprostinil (Remodulin®).

Pharmacodynamics—Antithrombin Agents or Other Antiplatelet Agents—Concomitant administration of TYVASO with diuretics, antithrombin agents or other antiplatelet agents may increase the risk of symptomatic hypotension. Anticoagulants—Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

Pharmacokinetics—Alcohol—In a human pharmacokinetic study conducted with orally administered treprostinil (Remodulin®), treprostinil does not inhibit cytochrome P450 (CYP3A4) isozyme and has a minimal effect on CYP2C9. In a human pharmacokinetic study conducted with orally administered treprostinil (Remodulin®) and an oral formulation of treprostinil (treprostinil diolamine), no pharmacokinetic interactions between treprostinil and bosentan were observed. Rifampin—a CYP2C9 enzyme inducer—in a human pharmacokinetic study conducted with subcutaneous (60 mg/day) and an oral formulation of treprostinil (treprostinil diolamine), no pharmacokinetic interactions between treprostinil and rifampin were observed. Effects of Cytotoxics—TYVASO inhibits platelet aggregation. In vitro studies of human hepatic microsomes showed that treprostinil did not inhibit cytochrome P450 (CYP) isozymes (CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2D6, CYP2E1 and CYP3A). Additionally, treprostinil does not induce cytochrome P450 isozymes (CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP3A) in human hepatocytes. In vivo studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) isozymes (CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP3A4) and does not increase the bioavailability of warfarin (10 ng/kg/min). Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S-warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

**USE IN SPECIFIC POPULATIONS**

Pregnancy—Pregnancy Category B—There are no adequate and well controlled studies with TYVASO in pregnant women. Animal reproduction studies have not been conducted with treprostinil administered by the inhalation route. However, studies in pregnant rabbits using continuous subcutaneous (sc) infusions of treprostinil sodium at infusion rates higher than the recommended human sc infusion rate resulted in an increased incidence of fetal skeletal variations associated with maternal toxicity. Animal reproduction studies are not always predictive of human response. Labor and Delivery—No treprostinil treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinil on labor and delivery in humans is unknown.

Nursing Mothers—It is not known whether treprostinil is excreted in human milk.

Pediatric Use—Safety and effectiveness in pediatric patients have not been established. Clinical studies of TYVASO did not include patients younger than 18 years to determine whether they respond differently from older patients.

Geriatric Use—Clinical studies of TYVASO 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 hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

Patients with Hepatic Insufficiency—Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects with mild- to-moderate hepatic insufficiency. Uptitrate slowly when treating patients with hepatic insufficiency because of the risk of an increase in systemic exposure which may lead to an increase in dose-dependent adverse effects. Treprostinil has not been studied in patients with severe hepatic insufficiency.

Patients with Renal Insufficiency—No studies have been performed in patients with renal insufficiency. Since treprostinil and its metabolites are excreted mainly through the urinary route, patients with renal insufficiency may have decreased clearance of the drug and its metabolites and consequently, dose-related adverse outcomes may be more frequent.

**OVERTOXIDATION**

In general, symptoms of overdose with TYVASO include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.

**PRECAUTIONS**

In general, avoid abrupt discontinuation of TYVASO. Patients should be monitored to detect any worsening of lung disease and loss of drug effect. If patients develop any new or worsening respiratory symptoms, such as cough, phlegm, sputum, or dyspnea, treatment should be adjusted to the lowest dose that maintains clinical benefit. If a patient's respiratory symptoms worsen, treatment discontinuation should be considered. Provide general supportive care until the symptoms of overdose have resolved.
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.

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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.
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 tadalafil 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 tadalafil, 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**: Tadalafil 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 (tadalafil) 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%).

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 monotherapy1,2

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 plans2

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

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%)

- Includes patients on monotherapy and background bosentan therapy1,2
- Clinical 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 class1
- 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.

www.adcirca.com  1-877-UNITHER

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Every Step Matters
ADCRICA® (tadalafil) tablets

BRIEF SUMMARY

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

INDICATIONS AND USAGE

Pulmonary Arterial Hypertension: ADCRICA is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity. Studies establishing effectiveness included predominantly patients with PAH-Functional Class II – III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

CONTRAINDICATIONS

Coadministration of Nitric Oxide Donors: Do not use ADCRICA in patients who are using any form of organic nitrate, either regularly or intermittently. ADCRICA potentiates the hypotensive effect of nitrates. This potentiation is thought to result from the combined effects of nitric oxide and tadalafil on the nitric oxide/cGMP pathway. Hypersensitivity Reactions: ADCRICA is contraindicated in patients with a known serious 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 ADCRICA. At least 48 hours should elapse after the last dose of ADCRICA before taking nitrites. If a patient has taken ADCRICA within 48 hours, administer nitrites under close medical supervision with continuous cardiac monitoring. Patients who have experienced anginal chest pain after taking ADCRICA 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 ADCRICA, 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 idiopathic hypertrophic subaortic stenosis) may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors. Pulmonary vasodilators may have contraindications to further use of these two drug classes on the nitric oxide/cGMP pathway.

Use with Alpha Blockers and Antihypertensives — PDE5 inhibitors, including tadalafil, have mild systemic vasodilatory properties that may result in transient decreases in blood pressure. Prior to prescribing ADCRICA, 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 idiopathic hypertrophic subaortic stenosis) may be particularly sensitive to the actions of vasodilators, including PDE5 inhibitors. Pulmonary vasodilators may have contraindications to further use of these two drug classes on the nitric oxide/cGMP pathway.

Use with Alcohol — Both alcohol and tadalafil are mild variables, including intravascular volume depletion and use of inhibitors and alpha blockers may be affected by other hypotension (e.g., fainting). Safety of combined use of PDE5 inhibitors with alcohol is not known, avoid use of both. Potent Inducers of CYP3A — For patients chronically taking potent inducers of CYP3A, such as rifampin, avoid use of ADCRICA.

Use in Renal Impairment: In patients with mild or moderate renal impairment — Start dosing at 20 mg once daily. Increase the dose to 40 mg once daily based upon individual tolerability. In patients with severe renal impairment — Avoid use of ADCRICA because of increased tadalafil exposure (AUC), limited clinical experience, and the lack of ability to influence clearance by dialysis.

Use in Hepatic Impairment: In patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B) — Because of limited clinical experience in patients with mild to moderate hepatic cirrhosis, consider a starting dose of 20 mg once daily ADCRICA. In patients with severe hepatic cirrhosis (Child-Pugh Class C) — Patients with severe hepatic cirrhosis have not been studied. Avoid use of ADCRICA.

Visual Loss: Physicians should advise patients to seek immediate medical attention in the event of a sudden loss of vision in one or both eyes. Such an event may be a sign of non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased vision, including permanent loss of vision that has been reported postmarketing in temporal association with the use of all PDE5 inhibitors. An observational study evaluated whether recent episodic use of PDE inhibitors, as a class, typical of erectile dysfunction treatment, was associated with acute onset of NAION. The results suggest an approximate 2-fold increase in the risk of NAION within 1 to 4 days of PDE inhibitor use. It is not possible to determine whether these events are related directly to the use of PDE inhibitors or other factors. Physicians should also discuss with patients the increased risk of NAION in individuals who have already experienced NAION in one eye, including whether such individuals could be adversely affected by use of vasodilators such as PDE5 inhibitors. Patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa, were not included in the clinical trials, and use in these patients is not recommended.

Hearing Impairment: Physicians should advise patients to seek immediate medical attention in the event of a sudden decrease or loss of hearing. These events, which may be accompanied by tinnitus and dizziness, have been reported in temporal association to the intake of PDE5 inhibitors, including ADCRICA. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors or to other factors.

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

Prolonged Erection: There have been rare reports of prolonged erections greater than 4 hours and priapism (painful erections 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. ADCRICA 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 anatomical deformations of the penis (such as angulation, curvature, or Peyronie’s disease).

Effects on Bleeding: ADCRICA is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. ADCRICA has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although ADCRICA 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

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of tadalafil. These events have been chosen for inclusion either because of their seriousness, reporting frequency, lack of clear alternative causation, or a combination of these factors. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reactions 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 ADCRICA, a total of 311 and 321 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 4% for ADCRICA 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 ADCRICA 40 mg was 4% compared to 5% in placebo-treated patients. In the placebo-controlled study, the most 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 ADCRICA 40 mg group and occurring more frequently than with placebo.

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ADCRICA 40 mg (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>flushing</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory Infection (Upper and Lower)</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Back Pain</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Nasol Constriction (Including sinus congestion)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
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 inhibits the cytochrome P450 system and increases tadalafil levels. Tadalafil is metabolized by cytochrome P450 3A4 systems. The coadministration of tadalafil with ritonavir may increase plasma levels of tadalafil, leading to a higher risk of adverse events.

Other Potent Inhibitors of CYP3A — Tadalafil is metabolized predominantly by CYP3A4 in the liver. The concomitant use of potent inhibitors of CYP3A such as ketaconazole, and fluconazole, may increase tadalafil levels and increase the risk of adverse events.

OTHER DRUG INTERACTIONS 

Use in Specific Populations: 

Pregnancy: 

Pregnancy Category B — Animal reproduction studies in rats and mice revealed no evidence of tadalafil-induced fetal harm. There are, however, no adequate and well-controlled studies 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-Breastfeeding Women: 

Tadalafil has been reported postmarketing in temporal association with cases of sudden decrease or loss of hearing. 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.

Use in Specific Populations: 

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Multiple patient types moving forward, one Adempas

In pulmonary arterial hypertension (PAH), (WHO Group 1)

**36m** improvement (mean) in 6-minute walk distance (6MWD) over placebo at Week 12 (95% Confidence Interval (CI): 20m-52m; p<0.0001)

Randomized, multicenter, placebo-controlled clinical study of 443 adult PAH patients with predominantly WHO Functional Class II–III. The primary endpoint was change from baseline in 6MWD at 12 weeks.

**INDICATIONS**

- 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%).

*Time to clinical worsening was a combined endpoint defined as death (all-cause mortality), heart/lung transplantation, atrial septostomy, hospitalization due to persistent worsening of pulmonary hypertension, start of new PAH-specific treatment, persistent decrease in 6MWD and persistent worsening of WHO functional class.

**CONTRAINDICATIONS**

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).

**WARNINGS AND PRECAUTIONS**

Embryofetal 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.

**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.

**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.

Please see additional Important Safety Information, including Boxed Warning, throughout and Brief Summary of Prescribing Information at end of advertisement.
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-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.

BAYER, the Bayer Cross, and Adempas are registered trademarks of Bayer.
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, 4.3, 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. [2.1, 2.3, 5.1, 8.6]
• 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 predominately 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 Nitrites 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 (7.1) and Clinical Pharmacology (12.2)].

4.3 Phosphodiesterase 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, hematnemesis, 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 (pooling 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>7</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) or 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, cilostazole, 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 smoke [see Doseage and Administration (2.4) and Clinical Pharmacology (12.3)].

Strong CYP3A4 and P-gp/BCRP inhibitors: Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-gp/BCRP inhibitors such as azole antifungals, diltiazem, verapamil, ketoconazole, itraconazole, P-gp or BCRP 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 during continuation of Adempas [see Doseage and Administration (2.4) and Clinical Pharmacology (12.3)].

Strong CYP3A inducers: Strong inducers of CYP3A4 (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 CYP3A3 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 toxicities with 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)].

Animal Data

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 humans. 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 (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 effectiveness were observed between elderly and younger subjects, 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 devices [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 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].

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 dialyzable.

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 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 (8.6)].
• 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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Program Announcement:

New Application Deadline: February 12, 2016
New Application Deadline: June 12, 2016
Resubmission Deadline: November 12, 2015
Resubmission Deadline: March 12, 2016

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 study 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 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.