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Advances in Pulmonary Hypertension

Chronic Thromboembolic Pulmonary Hypertension

Pulmonary Hypertension Care Centers
Murali Chakinala, MD; Michael McGoon, MD

Diagnosis and Preoperative Evaluation of Chronic Thromboembolic Pulmonary Hypertension
Coen van Kan, MD; Paul Bresser, MD, PhD

Pulmonary Endarterectomy: Assessment of Operability, Surgical Description, and Post-op Care
David Poch, MD; Victor Pretorius, MBchB

Medical Therapy for Chronic Thromboembolic Pulmonary Hypertension
Josanna Rodriguez-Lopez, MD; Richard N. Channick, MD

Pulmonary Hypertension Roundtable: CTEPH Experiences and Expertise

PHPN: Post-Pulmonary Endarterectomy: What to Expect During the First Year and How to Handle the Unexpected
Thao Drcar, NP

Ask the Expert: Do Patients With Pulmonary Arterial Hypertension Benefit From Referral to a Specialized Center?
Sean Studer, MD, MSc, FCCP
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Rita Orth, RN  Stanford Hospital  Stanford, California

Program Description
The mission of Advances in Pulmonary Hypertension is to serve as the premier forum for state of the art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension. The 2008 Dana Point revision of the World Health Organization Classification serves as a guide to categories of pulmonary hypertension addressed in Advances in Pulmonary Hypertension. While focusing on WHO Group 1 PAH, the other categories (Group 2, pulmonary venous hypertension; Group 3, associated with chronic lung disease and/or hypoxemia; Group 4, pulmonary embolic hypertension; Group 5, miscellaneous) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

Objectives
- Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension.
- Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.

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Michael D. McGoon, MD  Mayo Clinic  Rochester, Minnesota

The mission of the Scientific Leadership Council is to provide medical and scientific guidance and support to the PHA for:
- Developing and disseminating knowledge for diagnosing and treating pulmonary hypertension.
- Advocating for patients with pulmonary hypertension.
- Increasing involvement of basic and clinical researchers and practitioners.

More information on PHA’s Scientific Leadership Council and associated committees can be found at www.PHAssociation.org/SLC.
Submissions should be sent via e-mail as an attached Manuscript Preparation and Submission Process is determined by factors such as quality, relevance, and acceptance of manuscripts. Submitted manuscripts are reviewed by the editorial board. Acceptance of manuscripts for consideration by the Pulmonary Hypertension Association is independently determined by the Editor-in-Chief and the Editorial Advisory Board. While most articles are invited by the editorial board, the accepted manuscripts will be copy-edited and will be copy-righted by the Pulmonary Hypertension Association. Manuscripts are accepted for exclusive publication in Advances in Pulmonary Hypertension and will be copyrighted by the Pulmonary Hypertension Association. Articles and other selected healthcare professionals by the Pulmonary Hypertension Association. The contents of the articles are independently determined by the Editor-in-Chief and the Editorial Advisory Board. Articles are circulated to cardiologists, pulmonologists, rheumatologists, and other selected healthcare professionals by the Pulmonary Hypertension Association. The contents of the articles are independently determined by the Editor-in-Chief and the Editorial Advisory Board. Advances in Pulmonary Hypertension is available online at www.PHAssociation.org. Authors acknowledge all rights reserved. None of the contents may be reproduced in any form whatsoever without the written permission of PHA. Advances in Pulmonary Hypertension, Myung Park, MD, at mpark@medicine.umaryland.edu. 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. Any previously published figures, tables, etc. must contain material and must provide that material in reproducible form. Manuscripts are accepted for exclusive publication in Advances in Pulmonary Hypertension and will be copyrighted by the Pulmonary Hypertension Association. Conflict of Interest Disclosures A statement of any and all grant, contract, and industrial support or proprietary interests of the author(s) related to the subject matter must be submitted with the manuscript. Checklist Authors should be certain to include the following with the manuscript: 1. Title page listing all authors with their academic degree(s) and affiliations. 2. Corresponding author contact information including e-mail and phone number. 3. Copyright release form signed by all authors. 4. Conflict of Interest forms for all authors. 5. List of approximately 5 key words for indexing purposes. 6. Summary of the paper not exceeding 250 words in the format of Background; Objectives; Summary/Conclusions.
**EDITOR’S MEMO**

Diagnosis and Treatment of Chronic Thromboembolic Pulmonary Hypertension: An Era of Hope

Chronic thromboembolic pulmonary hypertension (CTEPH) may rank as one of the most underdiagnosed subsets among pulmonary hypertension categories. Designated as WHO Group 4 PH, CTEPH has been a notoriously difficult disease to determine from an epidemiological standpoint or to clearly elucidate mechanism and pathophysiology. CTEPH has also been shrouded in misconceptions and misunderstandings, such as whether a CT angiography is sufficient to evaluate CTEPH; or the relationship of a likelihood of presenting with CTEPH; or that pulmonary thromboendarterectomy (PTE) evaluation applies to some selected patients with CTEPH. Rather, we now know that a VQ scan is the test of choice to “rule out” and diagnose CTEPH; a good portion of patients do not have a history of prior pulmonary embolism when they present with CTEPH; and PTE should be considered for every patient who is diagnosed with CTEPH because it is the only form of PH that is potentially curable with a well-planned and appropriate surgical intervention.

It is thus my distinct pleasure to present this issue that focuses on the significant advances that have been made in diagnosing and treating this complex condition. I am very grateful to all the contributions of our Guest Editors, Dr. Richard Channick and Dr. Kim Kerr. They have assembled a renowned team of CTEPH experts to present the most current recommendations and emerging science focusing on diagnostic modalities, therapeutic considerations, and approaches—from specifics details of PTE surgery to discussing medical therapy with a focus on riociguat, which has been recently approved by FDA for treatment of patients with inoperable CTEPH or with recurrent PH post-PTE. The lively roundtable discussion, led by Dr. Channick, who is joined by Drs. Auger, McLaughlin, Pepke-Zaba, and Tapson, covers some of the controversial and difficult topics in treating patients with pulmonary thromboembolic disease such as thrombolysis and diagnostic dilemmas, to name a few.

Dr. Studer provides a thoughtful commentary on the role of specialized care centers in the management of CTEPH, and Ms. Dracar gives us the nuts and bolts of caring for patients post PTE surgery.

Finally, we have the pleasure of introducing the Pulmonary Hypertension Care Centers (PHCC) initiative by Drs. Chakinala and McGoon, the first of a series of articles that discusses the fundamental rationale and workings of this accreditation process.

I hope you find this issue enjoyable and helpful in your care of this challenging group of patients.

Myung H. Park, MD
Associate Professor of Medicine
Director, Pulmonary Vascular Disease Program
University of Maryland School of Medicine

(Continued on page 178)

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**GUEST EDITOR’S MEMO**

Chronic Thromboembolic Pulmonary Hypertension: Current Care

This issue of Advances in Pulmonary Hypertension is dedicated to the topic of chronic thromboembolic pulmonary hypertension (CTEPH). It is imperative that all healthcare providers who care for patients with pulmonary hypertension be aware of the appropriate screening tests and treatment of this disease as CTEPH is potentially curable with surgery.

Articles in this issue review the diagnostic evaluation, the surgical procedure of pulmonary thromboendarterectomy (PTE) (also referred to as pulmonary endarterectomy [PEA]), post-operative complications, care of surgical patients after hospital discharge, as well as the role of medical therapy of CTEPH.

Drs. Van Kan and Bresser provide an excellent and thorough review of the diagnosis and preoperative evaluation of CTEPH. Perfusion scintigraphy is highly sensitive for CTEPH, and is therefore the recommended screening test for this form of pulmonary hypertension. However, perfusion scans are not specific for CTEPH and, therefore, any patient with pulmonary hypertension and an abnormal perfusion scan should undergo further imaging such as CT angiography, pulmonary angiography, or MR angiography to establish the diagnosis of CTEPH and the location/operability of the clots. Echocardiography is also used as a screening test for the presence of pulmonary hypertension, followed by right heart catheterization to better quantify the hemodynamic impairment as well as the potential benefits and risks of surgery.

Drs. Poch and Pretorius review the topics of operability assessment, the PTE surgical procedure, and surgical outcomes. Determining operability requires an assessment of not just the location of the chronic thrombembolic lesions, but a clinical decision on whether the thrombus burden correlates with the degree of hemodynamic impairment, as well as diagnosing comorbidities that might affect surgical outcomes. This article, as well as the preceding article by Drs. van Kan and Bresser, stress that operability assessment should only be performed at experienced centers. The surgical technique is described, allowing readers to appreciate why this surgery should only be performed by surgeons with expertise in PTE surgery. In experienced hands, this procedure results in sustained significant hemodynamic and functional improvement with an acceptable mortality risk. The most common post-operative complications

(Continued on page 178)
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**INDICATIONS AND USAGE:** Letairis is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%).

**DOSAGE AND ADMINISTRATION:** Adult Dosage: Initial treatment at 5 mg once daily, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated. Tablets may be administered with or without food. Tablets should not be split, crushed, or chewed. Doses higher than 10 mg once daily have not been studied in patients with pulmonary arterial hypertension (PAH) (see Warnings and Precautions).

**CONTRAINdications:** Pregnancy: Letairis may cause fetal harm when administered to a pregnant female. Letairis is contraindicated in females of reproductive potential who are planning to become pregnant, are pregnant, or are breastfeeding. Letairis is available only through a restricted program called the Letairis REMS Program (see Warnings and Precautions). Exclusive pregnancy before the initiation of treatment with Letairis. Females of Reproductive Potential must use acceptable methods of contraception during treatment with Letairis and for one month after treatment. Obtain monthly pregnancy tests during treatment and 1 month after discontinuation of treatment (see Use in Specific Populations). Because of the risk of embryofetal toxicity, females can only receive Letairis through a restricted program called the Letairis REMS Program (see Warnings and Precautions).

**Use in Specific Populations:**

### ADVERSE REACTIONS:

**Most adverse drug reactions were mild to moderate and only nasal congestion was dose dependent.** The most frequent adverse reactions that occurred in >5% of patients receiving Letairis were: headache, nasopharyngitis, nasopharyngitis with impaction, rhinitis, cough, sinusitis, and peripheral edema. In clinical trials, peripheral edema was similar in younger patients (<65 years) receiving Letairis (14%; 292/205) and placebo (13%; 131/1,078), and was greater in elderly patients (≥65 years) receiving Letairis (29%; 156/541) compared to placebo (4%; 128). The results of such subgroup analyses must be interpreted with caution because these reactions related to PAH during the clinical trials in patients with PAH was similar for Letairis (2%; 5/261 patients) and placebo (3%; 1/312 patients). The incidence of patients with serious adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for placebo (12%; 13/104 patients) and for Letairis (13%; 28/205 patients). During 12-14 months of treatment, adverse reactions related to edema were reported in 8% of patients receiving Letairis. In placebo recipients, the incidence of anemia was 3%. Of the remaining 34 patients, one patient experienced a mild aminotransferase elevation at 12 weeks on Letairis 5 mg that resolved with decreasing the dose to 2.5 mg, and that did not recur with later dose escalations (14.9 h·μg/mL) based on AUC. In both species, there were abnormalities of the lower jaw and hard palate, malformation of the heart and great vessels, and failure of formation of the thymus and thyroid. A preclinical study in rats has shown decreased survival of newborn pups (mid and high doses) and effects on testis size and fertility of pups (high dose) following maternal treatment with ambrisentan from late gestation through weaning. Doses tested were 17X, 51X, and 170X (on a mg/kg/m² basis) the maximum oral human dose of 10 mg and an average adult body weight of 70 kg. Nursing Mothers: It is not known whether ambrisentan is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from Letairis, a decision should be made whether to discontinue nursing or to discontinue Letairis, taking into account the importance of the drug to the mother. Pediatric Use: Safety and effectiveness of Letairis in pediatric patients with PAH have not been established. Geriatric Use: In the two placebo controlled clinical studies of Letairis, 21% of patients were ≥65 years old and 5% were ≥75 years old. The elderly (≥65 years) showed no increase in adverse reactions compared to younger patients, but the results of such subgroup analyses must be interpreted cautiously. Peripheral edema was more common in the elderly than in younger patients. Females and Males of Reproductive Potential: Pregnancy Testing in Patients with Idiopathic Pulmonary Fibrosis (IPF) including IPF patients with pulmonary hypertension (IPF-PAH)**:

**Clinical studies included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%).**

**Clinical studies established effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%).**
Warning and Doseage and Administration/ Contraception: Female patients of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for 1 month after stopping treatment with Letairis. Patients may choose one highly effective form of contraception [intrauterine devices (IUD), contraceptive implants, or tubal sterilization] or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see Boxed Warning]. Infertility: Males In a 6-month study of another endothelin receptor antagonist, bosentan, 25 male patients with WHO functional class III and IV PAH and normal baseline sperm count were evaluated for effects on testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with bosentan. One patient developed oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Bosentan was discontinued and after 2 months the sperm count had returned to baseline levels. In 22 patients who completed 6 months of treatment, sperm count remained within the normal range and no changes in sperm morphology, sperm motility, or hormone levels were observed. Based on these findings and preclinical data [see Nonclinical Toxicology] from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as Letairis have an adverse effect on spermatogenesis. Counsel patients about the potential effects on fertility [see Warnings and Precautions]. Renal Impairment: The impact of renal impairment on the pharmacokinetics of ambrisentan has been examined using a population pharmacokinetic approach in PAH patients with creatinine clearances ranging between 20 and 150 mL/min. There was no significant impact of mild or moderate renal impairment on exposure to ambrisentan [see Clinical Pharmacology]. Dose adjustment of Letairis in patients with mild or moderate renal impairment is therefore not required. There is no information on the exposure to ambrisentan in patients with severe renal impairment. The impact of hemodialysis on the disposition of ambrisentan has not been investigated. Hepatic Impairment: Pre-existing hepatic impairment: The influence of pre-existing hepatic impairment on the pharmacokinetics of ambrisentan has not been evaluated. Because there is in vitro and in vivo evidence of significant metabolic and biliary contribution to the elimination of ambrisentan, hepatic impairment would be expected to have significant effects on the pharmacokinetics of ambrisentan [see Clinical Pharmacology]. Letairis is not recommended in patients with moderate or severe hepatic impairment. There is no information on the use of Letairis in patients with mild pre-existing impaired liver function; however, exposure to ambrisentan may be increased in these patients. Elevation of Liver Transaminases: Other endothelin receptor antagonists (ERAs) have been associated with aminotransferase (AST, ALT) elevations, hepatitis, and cases of liver failure [see Adverse Reactions]. In patients who develop hepatic impairment after Letairis initiation, the cause of liver injury should be fully investigated. Discontinue Letairis if aminotransferase elevations >5x ULN or if elevations are accompanied by bilirubin >3x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded. OVERDOSAGE: There is no experience with overdosage of Letairis. The highest single dose of Letairis administered to healthy volunteers was 100 mg and the highest daily dose administered to patients with PAH was 10 mg once daily. In healthy volunteers, single doses of 50 mg and 100 mg (5 to 10 times the maximum recommended dose) were associated with headache, flushing, dizziness, nausea, and nasal congestion. Massive overdosage could potentially result in hypotension that may require intervention. PATIENT COUNSELING INFORMATION: See FDA-approved patient labeling (Medication Guide). Embryo-fetal toxicity: Instruct patients on the risk of fetal harm when Letairis is used in pregnancy [see Warnings and Precautions, Use in Special Populations]. Female patients must enroll in the Letairis REMS Program. Instruct females of Reproductive Potential to immediately contact their physician if they suspect they may be pregnant. Letairis REMS Program: For female patients, Letairis is only available through a restricted program called the Letairis REMS [see Contraindications, Warnings and Precautions]. Male patients are not enrolled in the Letairis REMS. Inform female patients (and their guardians, if applicable) of the following notable requirements: All female patients must sign an enrollment form. Advise female patients of reproductive potential that they must comply with the pregnancy testing and contraception requirements [see Use in Special Populations]. Educate and counsel Females of Reproductive Potential on the use of emergency contraception in the event of unprotected sex or known or suspected contraceptive failure. Advise pre-pubertal females to report any changes in their reproductive status immediately to their prescriber. Review the Letairis Medication Guide and REMS educational material with female patients. A limited number of pharmacies are certified to dispense Letairis. Therefore, provide patients with the telephone number and website for information on how to obtain the product. Hepatic Effects: Some members of this pharmacological class are hepatotoxic. Patients should be educated on the symptoms of potential liver injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant abdominal discomfort, jaundice, dark urine or itching) and instructed to report any of these symptoms to their physician. Hematological Change: Patients should be advised of the importance of hemoglobin testing. Administration: Patients should be advised not to split, crush, or chew tablets. G522-081-012
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- **Scientific Sessions: New Treatments and Targets in Pulmonary Hypertension**
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ADDITIONAL INFORMATION

For PAH (WHO Group 1) patients on oral monotherapy

ADD MORE to your treatment strategy

+ PAH may be progressing even if patients seem stable1,2
+ Many patients plateau on oral therapy (PDE-5 inhibitor or ERA) within 12 weeks1,3,4

ADD MORE: Tyvaso is the only PAH treatment approved as an add-on to oral therapy5

+ After 1.7 years (mean) on oral monotherapy, adding Tyvaso for 12 weeks improved median 6MWD by 20 m (P=0.001)3,6
+ 4X daily dosing with short treatment sessions (2-3 minutes) approximately every 4 hours1,2

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 predominantly 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

+ 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 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 such as rifampin are added or withdrawn
+ 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%)

Tyvaso should be used in pregnancy only if clearly needed. Caution should be exercised when Tyvaso is administered to nursing women. See Boxed Warning in Full Prescribing Information.

References:

6MWD=6-minute walk distance. MLWHF=Minnesota Living With Heart Failure. NYHA=New York Heart Association. PAH=pulmonary arterial hypertension. WHO=World Health Organization.
BRIEF SUMMARY
The following is a brief summary of the full prescribing information for TYVASO® (treprostinil) Inhalation Solution. Please review the full prescribing information prior to prescribing TYVASO.

INDICATIONS AND USAGE
TYVASO is a prostanoyl 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 Treprostinil—Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure of both Cmax and AUC to treprostinil. Co-administration of a CYP2C8 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 (TRIUMPH I) of 235 patients with PAH (WHO Group I) and nearly all NYHA Functional Class III, the most commonly reported adverse reactions to 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>
<thead>
<tr>
<th>Common Adverse Reactions (%)</th>
<th>Placebo (%)</th>
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</tr>
<tr>
<td>Syncope 7 (6)</td>
<td>1 (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 one year. The adverse events during this chronic dosing study were qualitatively similar to those observed in the 12-week 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, pharyngolaryngeal pain, epistaxis, hemoptysis and wheezing. Serious adverse events during the open-label portion of the study included pneumonia in 8 subjects. There were three serious episodes of hemoptysis (one fatal) noted during the open-label experience.

DRUG INTERACTIONS
Pharmacokinetic/pharmacodynamic interaction studies have not been conducted with inhaled treprostinil (TYVASO); however, some of such studies have been conducted with orally (treprostinil diethanolamine) and subcutaneously administered treprostinil (Remodulin®).

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

- Pharmacokinetics—Bosentan—in a human pharmacokinetic study conducted with bosentan (250 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and bosentan were observed. Sildenafil—in a human pharmacokinetic study conducted with sildenafil (60 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and sildenafil were observed. Effect of Cytochrome P450 Inhibitors and Inducers—in vitro studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil increases exposure (both Cmax and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8. Effect of Other Drugs on Treprostinil—Drug interaction studies have been carried out with treprostinil (oral or subcutaneous) co-administered with etaminothiophene (4 g/day), warfarin (25 mg/day), and flecainide (200 mg/day), respectively in healthy volunteers. These studies did not show a clinically significant effect on the pharmacokinetics of treprostinil. Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of B- 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 (i.c.) 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; TYVASO should be used during pregnancy only if clearly needed.

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

- Nursing Mothers—It is not known whether treprostinil is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when treprostinil is administered to nursing women.

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.

Genetic 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 treprostinol 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.

OVERDOSAGE
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.

Table 1: Adverse Events in ≥3% of PAH Patients Receiving TYVASO and More Frequent* than Placebo
<table>
<thead>
<tr>
<th>Common Adverse Reactions (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough 62 (54)</td>
<td>35 (29)</td>
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PHA Online University is the premier online educational and networking resource for medical professionals seeking information about pulmonary hypertension, from diagnosis and treatment to the latest advances in the field.

At PHA Online University, healthcare professionals can:

- Earn free continuing education credits
- Access PHA’s quarterly medical journal, Advances in Pulmonary Hypertension
- Engage in worldwide networking and discussion among colleagues
- Participate in live webinars featuring leading experts in the field of PH
- Discover a wealth of valuable resources including recommendations for practice, treatment fact sheets, and abstracts and presentations from past medical education events

HIGHLIGHTED COURSE:

Chronic Thromboembolic Pulmonary Hypertension (CTEPH)
By Doug Helmersen, MD, FRCPC

Clinical Assistant Professor, Department of Medicine, University of Calgary
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 prostanooids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).
- OPSUMIT also reduced hospitalization for PAH.
- Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years.
  - Patients were treated with OPSUMIT monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanooids.
  - 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.*
**BRIEF SUMMARY**

The following is a brief summary of the full Prescribing Information for OPSUMIT® (macitentan). Please review the full Prescribing Information prior to prescribing OPSUMIT.

**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 REMS Program** [see Warnings and Precautions (OPSUMIT REMS Program)].

**INDICATIONS AND USAGE**

**Pulmonary Arterial Hypertension**

OPSUMIT is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group II) 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%).

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

**Embryo-fetal Toxicity**

OPSUMIT may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods and obtain monthly pregnancy tests [see Dosage and Administration section 2.2 in full Prescribing Information and Use in Specific Populations (Pregnancy, Females and Males of Reproductive Potential)].

OPSUMIT is available for females through the OPSUMIT REMS Program, a restricted distribution program [see Warnings and Precautions (OPSUMIT REMS Program)].

**OPSUMIT REMS Program**

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

Notable requirements of the OPSUMIT 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 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 [see Use in Specific Populations (Females and Males of Reproductive Potential)].
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive OPSUMIT.

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.

| Table 1: Incidence of Elevated Aminotransferases in the SERAPHIN Study |
|-----------------------------|-----------------------------|-----------------------------|
|                             | OPSUMIT 10 mg (N=242)       | Placebo (N=249)             |
| >3 x ULN                    | 3.4%                        | 4.5%                       |
| >8 x ULN                    | 2.1%                        | 0.4%                       |

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 x ULN, or by clinical symptoms of hepatotoxicity, discontinue OPSUMIT. Consider re-initiation of OPSUMIT when hepatic enzyme levels normalize in patients who have not experienced clinical symptoms of hepatotoxicity.

**Hemoglobin Decrease**

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

**Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)**

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

**Decreased Sperm Counts**

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

**ADVERSE REACTIONS**

Clinically significant adverse reactions that appear in other sections of the labeling include:
- Embryo-fetal Toxicity [see Warnings and Precautions (Embryo-fetal Toxicity)]
- Hepatotoxicity [see Warnings and Precautions (Hepatotoxicity)]
- Decrease in Hemoglobin [see Warnings and Precautions (Hemoglobin Decrease)]

**Clinical Trial Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Safety data for OPSUMIT were obtained primarily from one placebo-controlled clinical study in 742 patients with PAH (SERAPHIN study). The exposure to OPSUMIT in this trial was up to 3.6 years with a median exposure of about 2 years (N=542 for 1 year; N=429 for 2 years; and N=98 for more than 3 years). The overall incidence of treatment discontinuations because of adverse events was similar across OPSUMIT 10 mg and placebo treatment groups (approximately 11%).

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

| Table 2: Adverse Reactions |
|-----------------------------|-----------------------------|-----------------------------|
| Adverse Reaction            | OPSUMIT 10 mg (N=242)       | Placebo (N=249)             |
| Anemia                      | 13%                         | 3%                          |
| Nasopharyngitis/pharyngitis | 20%                         | 13%                         |
| Bronchitis                  | 12%                         | b%                          |
| Headache                    | 14%                         | 9%                          |
| Nfluenza                    | 6%                          | 2%                          |
| Urinary tract infection     | 9%                          | b%                          |

**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)].
**OPSUMIT® (macitentan)**

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

**Animal 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 OPUKOKIT 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 OPUSUMIT.

**Pediatric use**
The safety and efficacy of OPUSUMIT in children have not been established.

**Geriatric use**

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

**Females and Males of Reproductive Potential**

**Females**

**Pregnancy Testing:** Female patients of reproductive potential must have a negative pregnancy test prior to starting treatment with OPUSUMIT and monthly pregnancy tests during treatment with OPUSUMIT. Advise patients to contact their healthcare 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 OPUSUMIT and for 1 month after treatment with OPUSUMIT. Patients may choose one highly effective form of contraception (intraterine 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, OPUSUMIT may have an adverse effect on spermatogenesis [see Warnings and Precautions (Decreased Sperm Count) and Nonclinical Toxicology (Carcinogenesis, Mutagenesis, Impairment of Fertility)].

**OVERDOSAGE**

OPUSUMIT 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 (CrCl 15-29 mL/min) compared to healthy subjects was increased by 30% and 60%, respectively. This increase is not considered clinically relevant.

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

**Pharmacodynamics**

**Effect of other drugs on macitentan:** Use other PAH treatment options when strong CYP3A4 inhibitors are needed as part of HIV treatment [see Clinical Pharmacology (Pharmacokinetics)].

**Effect of other drugs on macitentan:** Macitentan is a substrate of CYP3A4, and its active metabolite is a substrate of CYP3A4 and BCRP. This enzyme inhibition is observed with macitentan at exposures of 12- to 116-fold the human exposure [see Drug Interactions (Strong CYP344 Inhibitors)].

**Contraindications (Pregnancy)**

Avoid concomitant use of OPUSUMIT with strong CYP3A4 inhibitors during treatment with OPUSUMIT and for 1 month after treatment with OPUSUMIT. Sildenafil and tadalafil are potent inhibitors of CYP3A4 and are contraindicated in combination with OPUSUMIT [see Drug Interactions (Strong CYP3A4 Inhibitors)].

**Use in Specific Populations**

**Hepatic impairment**

Severe renal impairment did not result in an increase in macitentan exposure at steady state similar to that seen with ketoconazole [see Drug Interactions (Strong CYP3A4 Inhibitors)].

**Special Populations**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

**Carcinogenesis:** Carcinogenicity studies of 2 years’ duration did not reveal any carcinoogenic 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 similar to the human exposure in 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.

**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**

**Interacting drug**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interacting medication</th>
<th>Active metabolite</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>Macitentan</td>
<td>Active metabolite</td>
<td>Avoid</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Macitentan</td>
<td>Active metabolite</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)].**

Manufactured for:

Actelion Pharmaceuticals US, Inc.  
5000 Shoreline Court, Ste. 200  
South San Francisco, CA 94080, USA  
ACT20131018


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April 26, 2014
Sonesta Hotel Philadelphia

1st Annual Drug Discovery and Development for Pulmonary Hypertension Symposium
July 15-16, 2014
Doubletree Hotel Bethesda
Bethesda, Md.

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Benefits Include:

- Receive unlimited access to PHA Online University, the premier online resource for PH education and CE-accredited courses about the diagnosis, treatment and advanced management of PH
- Attend the biennial International PH Conference and Scientific Sessions at a discounted price
- Host a Building Medical Education in PH event at your institution
- Receive updates on scientific findings and research opportunities through with PHA’s monthly e-newsletter PH Roundup
- Keep abreast of news and information on the entire PH community in Pathlight, PHA’s quarterly newsletter
- Connect directly with hundreds of knowledgeable PH-treating colleagues with PHCR and PHPN email groups
Our understanding and management of pulmonary arterial hypertension (PAH) has advanced tremendously over the last 30 years. Numerous scientific discoveries have helped to elucidate underlying mechanisms. Registries dating from the National Institutes of Health (NIH)-sponsored Patient Registry for Primary Pulmonary Hypertension (PPH Registry) of the 1980s to the recent REVEAL and French National registries have provided valuable information on PAH’s epidemiology, natural history, risk factors, and prognostic indicators. Clinical classifications and diagnostic algorithms have been developed and periodically updated through international collaboration. Most importantly, numerous pulmonary vasomodulating drugs have been developed, and their widespread use has been associated with longer survival and improved quality of life. Nevertheless, a cure remains elusive.

Increasing awareness of pulmonary hypertension (PH) and as pharmacologic therapies for PAH have become more accessible, the treatment paradigm has shifted from tertiary referral centers to a broad spectrum of medical practices. As a result, PH management is now delivered in a decentralized system by an increasing number of providers with varying degrees of expertise, leading to nonuniformity of care. Concomitantly, specific therapies have been applied to an increasingly diverse population of patients with PH. As a result, early access for patients to expert centers and assurances that optimal care is provided to all patients have become relevant concerns. Recent publications have highlighted these emerging challenges. In the RePHerral Study, conducted at 3 large university-based tertiary care referral centers in the United States, 98 of 140 referred patients had been assigned a definitive diagnosis of PAH before referral, but 32 (33%) were subsequently determined to be misdiagnosed. Forty-two patients were started on PAH-specific medications prior to referral, and 24 of these therapies were contrary to published guidelines. Fifty-nine patients had not had a pre-referral right heart catheterization. The PAH-QuERI project revealed underutilization of guideline-mandated studies for the evaluation of PH, especially the ventilation-perfusion scan and right heart catheterization. Additional literature spotlights some shortcomings in the management of PAH patients. Evidence suggests that patients followed outside of a referral center (compared with the individuals already under the referral center’s care) are treated with oral therapies longer, are more compromised and more likely to need urgent initiation of parenteral prostanoids, and have lower survival rates even after prostanoids are initiated. This raises the question of whether reliance on oral therapies by nonexpert centers delayed the appropriate and timely use of parenteral prostanoids. Evidence from the REVEAL Registry demonstrates that a substantial number of patients in functional class III or IV within 6 months of death had not received parenteral prostanoid at the time of death, suggesting possible underutilization of the most potent and effective class of therapies. Although these reports have shortcomings in terms of their small scale, retrospective design, or missing data, they appear to validate the perception of late recognition of PH, inaccurate diagnosis of PAH, untimely referral to expert centers, and inappropriate utilization of advanced therapies.

Two years ago, the Scientific Leadership Council (SLC) of the Pulmonary Hypertension Association (PHA) identified these emerging issues and advised its parent organization to develop and sponsor an accreditation program for PH centers in the US to harmonize and optimize management of PH. This course of action represented a shift in the PHA’s approach. Historically, PHA focused on growing the PH community in an effort to enhance disease awareness and patients’ access to care. But the evolving trends in health care delivery as described above have transformed PHA’s perspective and provided the resolve to
embark on this ambitious new course. A new initiative was spawned by the SLC’s recommendations: one that would help address the many challenges facing the PH community. The initiative’s mission statement is to establish a program of accredited centers with expertise in pulmonary hypertension that aspires to improve overall quality of care and ultimately improve outcomes of patients with pulmonary hypertension, particularly pulmonary arterial hypertension, a rare and life-threatening disease.

As a first step, the Pulmonary Hypertension Care Center (PHCC) Committee was formed and task forces were developed to: 1) develop criteria defining levels of expertise among centers, 2) explore funding, 3) formulate an implementation plan, and 4) design a patient registry. The PHCC Committee studied other disease-specific accreditation programs and benefitted greatly from understanding the organization and approach of the highly evolved and successful Cystic Fibrosis Foundation (CFF) Accredited Care Centers. Similar to CFF’s program, the overarching objective of the PHCC is to improve the overall care of patients, which should translate into better long-term patient outcomes. Such a challenging yet laudable goal can be accomplished through several interlocking components:

- Increasing disease awareness
- Improving access to expert care
- Raising the level of care at ALL centers through increased adherence to published guidelines and consensus statements
- Providing a blueprint to prospective programs for becoming PH care centers
- Fostering collaboration among expert centers for managing individual patients and cultivating new research opportunities in the field
- Conducting center-specific and national quality improvement projects with the aid of a national patient registry

Unlike the CFF program, which began decades ago in a time of few CF experts and no specific therapy, the PHCC is developing in an era with many more practitioners having varying levels of expertise, practicing in diverse environments, and using a number of FDA-approved PAH-specific therapies. Clearly, PH is managed much more diffusely than CF still is. Therefore, any plan for accreditation has to recognize this existing heterogeneity, especially when access to expert care is so vital for patients, while still holding centers accountable to a set of standards acceptable to the majority of stakeholders.

To face this challenge, the PHCC Committee has approached its mission with a spirit of inclusivity, and has incorporated flexibility in the criteria and evaluation methods. As an example, the number of actively managed patients expected at a PHCC, which understandably is a crude manner of assessing experience and expertise, is specified in the criteria but will be interpreted in the context of mitigating factors, such as duration of the program’s existence, regional population density, and proximity to other PH programs. In addition, the design for 2 types of centers (ie, Centers of Comprehensive Care [CCC] and Regional Clinical Programs [RCP]) is a central feature of the program that will hopefully maximize the eventual number of PHCCs across the country and enhance access to expert care. Both designations will be promoted.
as PHA-accredited PHCCs and will have to meet their respective criteria through the same application process and evaluation method. Both types of centers will have to broadly satisfy several categories of criteria, including center director, center coordinator, program staff/support services, facilities, and research (CCC only) (see Figure 1 and visit www.phassociation.org/phcarecenters for more details).

Although inclusivity is a point of emphasis, the criteria and accreditation program recognizes the need for adherence to standards for selection of PHCCs, so that the designation represents a tangible achievement and conveys meaningful information to the relevant stakeholders. Achieving the optimal balance of inclusivity and selectivity has been challenging for the PHCC Committee and, understandably, no system can fully satisfy all interested individuals. Accordingly, it is important to note that the aggregate PH community will continue to be architects of the program and have the opportunity, through a well-developed governance structure, to modify and update the system as necessary.

Clearly, the PHCC program will remain a work in progress for years to come. Other obstacles for the PHCC program include securing reliable funding to initiate and maintain the program, as well as designing a reasonable rollout program to meet the perceived heavy initial demand for accreditation. From the outset, the PHCC Committee and the SLC mandated that the PHCC be free of pharmaceutical industry influence in order for the program to credibly maintain fairness and impartiality. Therefore, funding for this complex and intricate program will be derived from other sources, while not competing with other important PHA endeavors. It is anticipated that funding will rely heavily on accreditation fees from prospective and existing centers, similar to other disease-specific certification programs, and through fundraising efforts geared toward individuals and foundations.

Moving forward, a sustainability committee will be assembled and will work with the PHCC governance structure to comprehensively procure new funding resources across the country.

The PHCC initiative already has generated tremendous interest in the United States, which is testimony to the perceived value of an accreditation program. By publicizing the criteria many months in advance, prospective centers will have an opportunity to enhance their respective programs. Significant demand and a large number of applications are anticipated once the program is inaugurated. In fact, an informal survey of PH Clinicians and Researchers (PHCR)/PH Professional Network (PHPN) membership in late 2013 revealed that at least 85 programs plan to apply for accreditation, with the majority hoping to apply in 2014. Accordingly, there is expectation of a flurry of applications to be received and site visits to be scheduled, with some unavoidable delay between application and accreditation (Figure 2).

To minimize delays in the process and avoid unintended advantages to the “early” applicants, a sizable review committee is being formed and the program’s accreditation announcements will likely occur in a batched manner that is still under discussion.

As the PHA and the PH community is on the cusp of launching this exciting and much needed grassroots program for accrediting PHCCs, it is vital to appreciate the enormity of the project and its potential consequences without becoming paralyzed by fear and uncertainty. For the sake of our patients, the PH community needs to find the courage and perseverance to forge ahead. In the next few issues of Advances in Pulmonary Hypertension, there will be additional updates about the PHCC program that will coincide with the PHCC’s activities and milestones in the coming year.
References

Guest Editor’s Memo
(continued from page 162)

are hypoxemia and reperfusion lung injury, best managed by a multidisciplinary team.

The role of medical therapy for CTEPH is outlined in a very thorough review of the related literature by Drs. Rodriguez-Lopez and Channick. This is an important article given the observation that, despite lack of convincing data, the use of medical therapy for CTEPH prior to PTE has increased substantially over the past decade, culminating in the approval of a medication for patients with inoperable CTEPH or recurrent/persistent CTEPH following PTE.

This issue also includes a lively roundtable discussion by international CTEPH experts pondering many of the unanswered questions and debated issues surrounding CTEPH.

We hope you find this issue of Advances useful, and that it raises awareness and knowledge of this important disorder.

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Diagnosis and Preoperative Evaluation of Chronic Thromboembolic Pulmonary Hypertension

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Chronic thromboembolic pulmonary hypertension (CTEPH) can be defined as precapillary pulmonary hypertension (PH) as assessed by right heart catheterization, and results from incomplete resolution of the vascular obstruction associated with acute pulmonary embolism (PE). Pulmonary thromboendarterectomy (PTE) is the therapy of choice for CTEPH patients with surgically accessible thrombi. Although associated with potential risks, PTE has been found to improve, and in many cases normalize pulmonary hemodynamics, functional status, and long-term survival. It is critical to undergo careful diagnosis and preoperative selection of patients who will most likely benefit from surgery. We have used published literature along with our personal experiences to review diagnosis of CTEPH and evaluation in advance of the PTE procedure.

In patients with PH or suspected PH, a complete diagnostic workup should be performed to identify the underlying etiology of the disease. Pulmonary angiography and right heart catheterization are the preferred assessment tools to diagnose CTEPH. PTE remains the treatment of choice, and for further evaluation of operability and preoperative risk patients should be referred to a CTEPH expert center.

Chronic thromboembolic pulmonary hypertension (CTEPH) results from incomplete resolution of the vascular obstruction associated with acute pulmonary embolism (PE). CTEPH can be defined as precapillary pulmonary hypertension (PH) as assessed by right heart catheterization, ie, mean pulmonary arterial pressure (mPAP) ≥25 mm Hg and pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg, in the presence of multiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries after at least 3 months of effective anticoagulation. CTEPH is considered to develop in 1% to 4% of patients who survive an acute PE. In a recent prospective study in patients with newly diagnosed CTEPH, a history of acute PE was confirmed in 74.8% of the patients included. In CTEPH patients without evidence for a previous acute PE episode, clinical risk factors that have been identified for developing CTEPH include ventriculoatrial shunt, indwelling catheters and leads, splenectomy, thyroid replacement therapy, inflammatory bowel disease, and a history of malignancy. Abnormalities in coagulation and fibrinolysis pathways have been associated in the minority of CTEPH patients, with the most prevalent ones being lupus anticoagulant and antiphospholipid antibodies. Increased levels of factor VIII, which is a risk factor for recurrent PE, have been shown to be present in patients with CTEPH as compared to healthy subjects and patients with other forms of PH.

If left untreated, CTEPH is a progressive and life-threatening disorder, with survival being proportional to the degree of PH at the time of diagnosis. Over time, a gradual hemodynamic and symptomatic decline can be observed in CTEPH patients, which appears to be related to the development of a secondary pulmonary hypertensive arteriopathy in the small nonobstructed precapillary pulmonary vessels. As a consequence, prognosis is in major part determined by the progression of this arteriopathy.

Pulmonary thromboendarterectomy (PTE) is the therapy of choice for CTEPH patients with surgically accessible thrombi, which essentially offers a chance to cure the disease. PTE has been found to improve, and in many cases normalize pulmonary hemodynamics, functional status, and long-term survival. The surgery, however, does not come without potential risk. Reported peri- and direct postoperative mortality vary between PTE centers, with 2% to 3% even in the most experienced centers. Therefore, it is critical to undergo careful diagnosis and preoperative selection of patients who will most likely benefit from surgery.

CLINICAL PRESENTATION

Most CTEPH patients present with gradually progressive exercise intolerance, typically portrayed as exertional dyspnea, fatigue, palpitations, and/or a nonproductive cough. Occasionally, patients may present with hemoptysis originating from hypertrophied bronchial arteries. The exercise intolerance is in major part caused by the inability of the heart to sufficiently increase pulmonary blood flow due to a decreased right ventricular (RV) stroke volume response during exercise. As blood flow fails to perfuse the ventilated lung, dead space ventilation will increase; to compensate

Key Words—pulmonary hypertension, thromboembolism, pulmonary endarterectomy, diagnosis, preoperative evaluation

Disclosure: Paul Bresser received honoraria for lecturing at conferences from Actelion Pharmaceuticals, Nederland bv, Woerden, the Netherlands. Dr van Kan states that no conflict of interest exists.
for this increase the patient’s ventilatory requirement must increase. At the same time, the inability to increase cardiac output impairs oxygen transport appropriately in response to exercise, causing a low work rate “lactic acidosis” and exercise-induced hypoxemia, both further stimulating the ventilatory drive. In more advanced stages of disease there may be signs of RV failure, chest pain on exertion, and syncope. The ensuing progressive RV failure leads to worsening disability and early death.

On physical examination of the heart, prolongation of the second heart sound with a fixed accentuated P2 is characteristic for a late closure of the pulmonary valve due to RV overload; a tricuspid insufficiency murmur is often present. Over the lungs in approximately 30% of patients a bruit can be heard, representing flow turbulence in the compromised, partially occluded pulmonary vessels. This pulmonary flow murmur is a finding specific to CTEPH, not seen in other forms of PAH. Evaluation of ECG can show signs of RV overload, which include right axis deviation and T-wave inversion in V1-V5.

Chest x-ray is remarkably normal in many CTEPH patients. In a more advanced state of the disease, enlargement of the proximal pulmonary vasculature can be observed; depending on the arteries involved, this finding can be asymmetric. Also, signs of right heart chamber enlargement, such as an enlarged right heart border and obliteration of the retrosternal space may be observed. The parenchyma of the lung may show areas of relative hypoperfusion or may show evidence for previous lung infarction.

Pulmonary function testing does not show a specific CTEPH pattern. Lung volumes and spirometry are generally within normal limits. Diffusion capacity for carbon dioxide may be normal or slightly reduced. It is, however, of use in the preoperative workup, evaluating coexisting emphysema or interstitial lung disease.

**DIAGNOSTIC WORKUP OF CTEPH**

The diagnostic workup and preoperative evaluation in patients suspected to suffer from CTEPH are based on 3 pillars: 1) the presence of PH and chronic thromboembolism needs to be established and the hemodynamic severity of the disease must be determined; 2) the operability in terms of surgical accessibility of the chronic thromboemboli needs to be assessed; and 3) a thorough preoperative risk assessment must be made. Transthoracic echocardiography is of major importance to define the presence and severity of the PH. The echocardiogram typically demonstrates variable degrees of RV dilatation and hypertrophy. The interventricular septum may be flattened and often exhibits paradoxical motion, with encroachment of the septum into the left ventricle. Variable degrees of tricuspid regurgitation can be present. The peak systolic pulmonary artery pressure (sPAP) can be estimated using the modified Bernoulli equation.
shortened pulmonary acceleration time can give additional information on elevated pulmonary pressures.\textsuperscript{21} Echocardiography may also demonstrate the presence of a patent foramen ovale, an atrial or ventricular septal defect, or concomitant left heart disease. Exercise characteristically increases PH in these patients. Therefore, in patients with only mild abnormalities at rest, performing exercise echocardiography has been suggested to assess hemodynamic response to activity. However, the application and utility of exercise echocardiography in diagnosing PH still needs confirmation by prospective studies.\textsuperscript{3,22}

Radioisotope ventilation-perfusion (V/Q) scintigraphy is absolutely essential to the diagnostic evaluation of PH and is the most crucial test in determining the presence of thromboembolism. A normal V/Q scan practically rules out chronic thromboembolic disease as cause of PH. In CTEPH patients, it typically shows multiple lobar and/or segmental perfusion defects (Figure 1). Perfusion scintigraphy, however, tends to underestimate the degree of vascular obstruction. Therefore, in the workup of patients with PH, an equivocal scan needs further evaluation by pulmonary angiography.\textsuperscript{23,24} It should be emphasized that there is no substitute for the V/Q scan in the diagnosis of CTEPH with its near 100\% sensitivity. However, indistinguishable patterns of V/Q defects have been reported in patients with extrinsic pulmonary vascular compression from mediastinal lymphadenopathy or fibrosis, primary pulmonary vascular tumors, and large-vessel pulmonary arteritis.\textsuperscript{25} V/Q scintigraphy in case of distal pulmonary vascular disease most frequently will show a mottled appearance, with the exception of pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis, in which the perfusion scan may show lobar and/or segmental defects.\textsuperscript{26,27}

If chronic thromboembolism is considered to be present, pulmonary angiography is mandatory to confirm the presence of PH and to establish its chronic thromboembolic nature. Moreover, it is used to determine whether the chronic thromboembolic obstruction is surgically accessible. When biplane angiography is performed, this will in the majority of cases provide adequate information on lobar and segmental anatomy to determine the surgical accessibility. Angiographic findings in CTEPH differ from the findings in acute PE. In CTEPH, the radiographic abnormalities reflect different patterns of organization and recanalization of emboli. Pouches, stenosis with or without post-stenotic dilatation, intimal irregularities, webs, and bands are the classic angiographic abnormalities seen in CTEPH (Figure 2). Pulmonary angiography can be combined with right heart catheterization to establish the hemodynamic severity of disease, and it provides essential information on cardiac function. In addition, measurements of oxygen saturations in the vena cava, right heart chambers, and the pulmonary artery may reveal previously undetected intracardiac shunting. In patients at risk for coronary artery disease, simultaneous coronary angiography should be considered, as combining coronary artery bypass grafting with PTE, as well as valve repair, can be performed in most patients with similar perioperative risk.\textsuperscript{28} Although the combined “classic” biplane pulmonary angiography with right heart catheterization are considered the gold standard for diagnosing CTEPH in most expert centers, some of the recently developed diagnostic modalities are also utilized to provide additional information. Contrast-enhanced computed tomography (CT) angiography is performed, as it may add information on vascular obstructions in the main stem of both pulmonary arteries, which can be missed by conventional angiography (Figure 3). It also provides additional information on the lung parenchyma and mediastinal structures, so can be used to study the presence of other conditions which may mimic chronic thromboembolism.\textsuperscript{29,30} In CTEPH, CT angiography may show organized thrombi in the (proximal) pulmonary arteries, abrupt tapering of vessels, intimal irregularities, and webs. In addition, next to the PH-associated dilatation of the central pulmonary arteries and right heart chambers, post-PE scarring in underperfused lung areas can result in a mosaic pattern of perfusion obstruction.

Figure 2: Right and left pulmonary angiography in the patient from Figure 1, demonstrating occlusion of the pulmonary arteries to the middle lobe and the right and left lower lobes due to chronic thromboembolism manifesting as pouches (black arrows).
and the presence of collateral vessels arising from the bronchial arterial circulation that point to the diagnosis.\textsuperscript{31,32} In CTEPH patients, the presence of dilated bronchial artery collaterals was shown to be associated with a better postoperative outcome, ie, a lower postoperative pulmonary vascular resistance (PVR) and a lower mortality.\textsuperscript{33}

The most recent CT modalities, combined with the increase in experience using the technique, show favorable sensitivity levels in evaluating CTEPH. While promising, V/Q scan is the test of choice to definitely "rule out" and diagnose CTEPH. Further prospective confirmation is needed before recommendations can be given regarding the utility of the CT.\textsuperscript{34,35} A radiographic pitfall of particular interest that can be appreciated on CT angiography is "non-obstructive in-situ pulmonary artery thrombosis," which may occur in idiopathic pulmonary arterial hypertension (PAH) and may mimic pulmonary artery occlusion due to chronic thromboembolic disease. Operative removal of these clots must be avoided since it will not result in hemodynamic improvement.\textsuperscript{36} It is recommended that if there is a question regarding whether the findings represent CTEPH or PAH with thrombus in situ, the images should be referred for review by an expert center.

Additionally, advances in imaging techniques in magnetic resonance angiography (MRA) have been developed in CTEPH. Contrast-enhanced MRA can be used for morphological assessment of the pulmonary vasculature, and has been shown to demonstrate the typical features of chronic thromboembolic disease. However, the interpretation of these features solely by means of MRA has shown low sensitivity levels as compared to conventional pulmonary angiography.\textsuperscript{37,38} Other potential uses of magnetic resonance imaging (MRI) include the structural and functional assessment of the heart, as it may provide information on end-systolic and diastolic volumes, ejection fraction, and muscle mass.\textsuperscript{39} In this respect cardiac MRI has been used to study cardiac (dys)function in CTEPH patients, and it was used to demonstrate the restoration of RV remodelling and function after hemodynamically successful PTE (Figure 4).\textsuperscript{40,41} In addition, 3D contrast-enhanced lung perfusion MRI may provide insight into regional pulmonary perfusion by tracking the dynamic passage of a contrast bolus. Although no comparison with the standard of reference was made, in a recent study in 68 patients with proven CTEPH, 3D contrast-enhanced lung perfusion MRI showed a sensitivity of 97% for the diagnosis of chronic thromboembolic disease, as compared to CT angiography (94%) and perfusion scanning (96%).\textsuperscript{32} Despite these promising results, definitive data on direct comparison of MRA with conventional biplane angiography are still lacking.

Although studies using CT angiography and MRA may indicate that both modalities can be used to evaluate for presence of chronic thromboembolic disease and to obtain additional relevant information, currently both techniques still appear to underestimate the degree of the vascular obstruction.\textsuperscript{2} In particular, the absence of reported radiographic abnormalities does not rule out surgically accessible chronic thromboembolic disease.\textsuperscript{11} As noted before, in patients with proven chronic thromboembolic disease without evidence for PH at rest, consideration for pursuing additional investigations to evaluate exercise hemodynamics have been suggested to evaluate for presence of a possible exercise-induced compromised pulmonary circulation. However, this approach needs to be studied further.

**PREOPERATIVE EVALUATION**

In general, patients undergoing PTE typically exhibit a preoperative PVR >300 dynes\textsuperscript{-s} cm\textsuperscript{-5}, usually in the range of 800-1200 dynes\textsuperscript{-s} cm\textsuperscript{-5}, at rest or during exercise.\textsuperscript{11,43} Currently, the
Secondly, prediction of operable in highly experienced...embolic occlusions of segmental and/or pulmonary arteries. Chronic thromboembolic pulmonary hypertension: utility of magnetic resonance imaging to demonstrate restoration of the right ventricle. J Thorac Cardiovasc Surg. 2007;133(1):58-64 with permission from Elsevier.

For assessment of the relative contribution of a small vessel component to the PVR, the previously reported pulmonary artery occlusion technique represents a promising option. It is based on the assumption that the decaying pulmonary arterial occlusion pressure waveform can be used to estimate precapillary pressures; the PVR can then be partitioned into large arterial (upstream) and small arterial plus venous (downstream) components. An inverse correlation has been demonstrated between the percent of upstream resistance and postoperative mPAP and PVR. This technique, however, is technically highly challenging and still needs further clinical validation. An alternative and simpler method to distinguish proximal from distal disease uses a particular feature of the Doppler-derived pulmonary flow profile. The midystolic deceleration in pulmonary flow, the so-called pulmonary flow systolic notch, was shown to occur significantly later during the systole in patients with idiopathic PAH as compared to patients with proximal PE. In a dog model, compared to constriction of proximal pulmonary arteries, experimentally induced microembolization of distal pulmonary arteries resulted in a later notch. In CTEPH patients who underwent PTE, we showed that a late notch defined as a notch ratio >1 was indeed associated with a higher risk for persistent PH and an increased in-hospital mortality.

In addition, risk for adverse outcome after PTE has been attributed to various comorbid factors, in particular the coexistence of chronic obstructive or restrictive lung disease. Revascularization of lung areas with emphysema or interstitial lung disease may be associated with marked postoperative hypoxemia, thereby decreasing the PTE-associated hemodynamic benefits. Moreover, age, marked obesity, renal or hepatic insufficiency, and malignancy with a reasonable life expectancy should be taken into consideration, but none of these factors should pose an absolute contraindication for surgery.

Although patients with proximal
CTEPH may benefit from medical treatment,\textsuperscript{2,5,55-57} medical pretreatment prior to PTE is not indicated in the vast majority of patients. It is recommended that whenever possible PTE should be performed without any delay.\textsuperscript{28} Furthermore, medical treatment may never be considered an alternative for PTE in patients with surgically accessible and thereby curable CTEPH. A full discussion regarding medical therapy for inoperable and recurrent PH in CTEPH is covered elsewhere in this issue.

CONCLUSION
In patients with PH or suspected to suffer from PH, diagnostic workup including V/Q scintigraphy should be performed to elucidate the underlying etiology. In case of an abnormal V/Q scan, pulmonary angiography and right heart catheterization are the gold standard for diagnosing CTEPH. PTE is the treatment of first choice, and for further evaluation of operability and preoperative risk patients should be referred to a CTEPH expert center.

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Pulmonary Endarterectomy: Assessment of Operability, Surgical Description, and Post-op Care

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Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as a mean pulmonary artery pressure ≥25 mm Hg and pulmonary artery wedge pressure ≤15 mm Hg in the presence of occlusive thrombi within the pulmonary arteries. Surgical pulmonary thromboendarterectomy (PTE) is considered the best treatment option for CTEPH.

PTE is a technically difficult procedure that requires careful patient selection, surgical experience, and high level of postoperative care to be successful. We have used published literature in tandem with our experience to review operability assessment criteria, detail some specifics of PTE surgical technique, and offer considerations for postoperative care.

Surgical PTE remains the top treatment for CTEPH. Once a diagnosis of CTEPH is made, it must be determined whether the patient will benefit from PTE surgery and if the benefits will outweigh the associated risks. All CTEPH patients should be considered for surgery, and no patient should be turned down without consultation with an experienced center. The success of the surgery owes as much to appropriate patient selection as it does to surgical technique and postoperative management. No level of pulmonary hypertension or degree of right heart failure is a contraindication to surgery, and excellent short- and long-term results can be achieved with adherence to established surgical principles.

Chronic thromboembolic pulmonary hypertension (CTEPH), currently categorized as World Health Organization (WHO) Group 4, is defined as a mean pulmonary artery pressure ≥25 mm Hg and pulmonary artery wedge pressure ≤15 mm Hg in the presence of occlusive thrombi within the pulmonary arteries. Surgical pulmonary thromboendarterectomy (PTE) remains the gold standard treatment for CTEPH. Patients who undergo PTE have improved 3-year survival (89% vs 70%) compared with nonoperated patients treated with medical therapy. Surgery typically results in a greater mean reduction in pulmonary vascular resistance (PVR) than can be achieved with medical therapy. PTE is a technically difficult procedure that requires careful patient selection, surgical experience, and high level of postoperative care to be successful.

**ASSESSMENT OF OPERABILITY**

Once a diagnosis of CTEPH is made, the crucial decision, and often the most difficult, is determining if the specific patient will benefit from PTE surgery and if the benefits will outweigh the associated risks. PTE is the only treatment with a potential cure and therefore the treatment of choice for CTEPH. All CTEPH patients should be considered for surgery, and no patient should be turned down without consultation with an experienced center. Much has been learned over the past decade and has improved the operative safety of PTE surgery, which is now considered a relatively safe procedure with an experienced team, with in-hospital mortality rates of 2.2% (at a single US referral center) and 4.7% (across multiple European centers performing PTE). The success of the surgery owes as much to appropriate patient selection as it does to surgical technique and postoperative management. The determination of operability relies on 3 key assessments:

1. Does the clot burden observed on imaging correlate with the degree of hemodynamic impairment observed during right heart catheterization?
2. Are the diseased vessels surgically accessible?
3. Does the patient have comorbidities that would prohibit PTE surgery?

Correlating clot burden with hemodynamic impairment can be difficult. This is particularly true for patients with Type III disease (segmental level disease) and advanced right heart failure. When considering operability, the goal is to identify sufficient accessible disease so PTE surgery results in a reduction of PVR near or within the normal range. In large series published from the United States and Europe, the mean and median improvements in PVR typically achieve a postoperative PVR <300 dyne·s·cm⁻².3,4

While centers have reported higher mortality in patients with preoperative PVR >1200 dyne·s·cm⁻²,5,5 this finding is not a contraindication to PTE and should not limit referral to a CTEPH.
center for surgical evaluation. In fact, this is the group of patients that requires particular care during evaluation and should be referred to an experienced CTEPH center. Under the care of a team with expertise in CTEPH, with correct patient selection, patients with preoperative PVR >1200 dynes·sec·cm⁻⁵ can be operated with good outcomes.

Recent data from the University of California San Diego (UCSD) demonstrated a mortality of 4.1% for patients with preoperative PVR >1000 dynes·sec·cm⁻⁵ compared with 1.6% for PVR <1000 dynes·sec·cm⁻⁵. Persistent pulmonary hypertension (PH) following PTE has a much more dramatic influence on operative and 1-year mortality than elevated preoperative PVR. In 500 consecutive cases performed at UCSD, mortality was 10.3% for patients with a postoperative PVR >500 dynes·sec·cm⁻⁵ compared with 0.9% for patients with a postoperative PVR <500 dynes·sec·cm⁻⁵. All efforts should be made to perform complete endarterectomy to avoid persistent PH.

Distal location of thrombotic material and thus surgical accessibility plays a significant role in determining operability. Type III disease, where thrombi are located at the segmental and subsegmental level, is increasingly considered operable but requires a particularly high level of surgical expertise. At UCSD, among a series of 121 consecutive type III disease cases, the mean postoperative PVR was 286 dynes·sec·cm⁻⁵ and hospital mortality 1.7%.

Based on data from the European CTEPH registry, coronary artery disease increases in the hospital and 1-year mortality associated with the surgery from 2.1% to 10% and 5.1% to 15% respectively. Other factors that make the surgery technically more difficult but have not been shown to increase mortality include elevated body mass index (BMI), taller patient height, and the presence of prior sternotomy.

**Surgical Technique**

There are 3 guiding principles for the operation:

I. The endarterectomy should be bilateral, performed via a median sternotomy.

II. Cardiopulmonary bypass is essential to ensure cardiovascular stability when the operation is performed and to cool the patient to allow circulatory arrest.

III. A bloodless field is required to define an adequate endarterectomy plane and to then follow the pulmonary endarterectomy specimen deep into the subsegmental vessels. Bronchial blood flow can be copious in these cases, and therefore periods of circulatory arrest are necessary to ensure optimal visibility. The circulatory arrest periods are limited to 20 minutes, with restoration of flow between each arrest for a minimum of 10 minutes.
Much of the preoperative preparation is common to any open-heart procedure. Following median sternotomy, expect to find an enlarged right heart with a tense right atrium. After full heparinization, wire-reinforced flexible cannulas are used for high ascending aortic and bicaval cannulation and institution of full cardiopulmonary bypass. Temporary pulmonary artery and left atrial vents are placed.

In addition to cooling the blood via the heater-cooler, surface cooling with both a head ice-jacket and a cooling blanket is initiated. Gradual cooling with a 10°C gradient ensures uniform tissue cooling and generally takes 45 to 60 minutes. At a core temperature of 20°C, the aorta is cross-clamped and a single dose (1 L) of cold blood cardioplegic solution is administered. A cooling jacket wrapped around the heart offers additional myocardial protection.

The superior vena cava is circumferentially mobilized. The approach to the right pulmonary artery is made medial to the superior vena cava. All dissection of the pulmonary arteries is carried out intra-pericardially. An incision is made in the right pulmonary artery under the superior vena cava and entering the lower lobe branch. When blood obscures direct vision, circulatory arrest is initiated, and the patient is exsanguinated (Figure 1).

Dissection in the correct plane is critical, as dissection too deep will result in vessel perforation and consequent airway bleeding. Dissection that is too superficial will result in failure to remove all thrombotic material. Once the plane is correctly developed, the endarterectomy is performed with an eversion technique. It is important that each subsegmental branch is followed and freed individually until it ends in a tail beyond which there is no further obstruction.

Jamieson classified pulmonary occlusive disease into 4 types (Figure 2):

I. Type I disease refers to major vessel clot present and readily visible upon opening the pulmonary arteries.

II. Type II disease findings are: thickened intima, webs, and bands. Here, the endarterectomy plane is raised in the main, lobar, or segmental vessels.

III. Type III disease is very distal and confined to the segmental and subsegmental branches.

IV. Type IV disease affects intrinsic small vessels and is inoperable, although secondary thrombus can occur as a result of stasis.

Once the right-sided endarterectomy is completed, circulation is restarted, and the arteriotomy is repaired. It is important that this suture line is hemostatic because visualization is extremely difficult once the patient is weaned from bypass.

For the left endarterectomy, the heart is retracted to an inferior-medial position with the aid of a heart net while still keeping the heart wrapped in the cooling jacket. The left-sided dissection and repair are analogous to that accomplished on the right.

After the endarterectomy is completed, cardiopulmonary bypass is reinstituted and warming is commenced. Methylprednisolone (500 mg) and mannitol (12.5 g) are administered to minimize capillary leak following prolonged cardiopulmonary bypass. If other cardiac procedures are required, these are conveniently performed during the rewarming period. Weaning from bypass and wound closure is routine.

**POSTOPERATIVE CARE**

**Standard Care**

Much of the postoperative care is similar to that of other open-heart surgery patients, with focus on hemodynamic support, volume management, and optimizing oxygenation. Patients remain on mechanical ventilation until postoperative day 1 when assessments for extubation are performed. The additional time spent on mechanical ventilation allows additional time to monitor for bleeding, and most importantly early reperfusion pulmonary edema.

Pneumatic compression devices are used for venous thrombosis prophylaxis immediately following surgery. Anticoagulation is initiated a few hours following surgery once chest tube drainage and bleeding is at a minimum. The patient’s risk for rethrombosis dictates the agent used for anticoagulation and the therapeutic target.

For patients considered low risk for rethrombosis, heparin at venous thrombosis prophylaxis levels is used until the pacing wires are removed. The majority of patients immediately post-op are placed on heparin subcutaneously at doses that are usually used for deep venous thrombosis (DVT) prophylaxis. The subcutaneous heparin is started once...
chest tube output drainage has slowed. A typical starting point for subcutaneous heparin administration is when the output is <25 mL/hr for 4 hours. The typical dose is heparin 5,000 units subcutaneously for 8 hours, and is sometimes adjusted up or down if patients are very small or very large, but this adjustment is aimed at achieving DVT prophylaxis levels of drug. For patients who are at higher risk of post-op rethrombosis, intravenous heparin is used instead of subcutaneous heparin, and the target partial thromboplastin time (PTT) or XA levels are those used for DVT/pulmonary embolism (PE) treatment (PTT 60-80).

There is some “artistry” in the choice of PTT target and method of heparin titration. Once the pacing wires are removed and chest tube drainage is at a minimum, warfarin is initiated. For patients taking aspirin in addition to warfarin, the target international normalized ratio (INR) is typically 2-3, and a higher target of 2.5-3.5 is encouraged for all other patients. Currently warfarin- or heparin-based anticoagulation is recommended for the first 6 months following surgery. Newer oral direct thrombin inhibitors may be used after 6 months, but experience with these agents in CTEPH is currently limited.

Patients with intracardiac thrombi, complete obstruction of a main pulmonary artery, unilateral occlusion, and high titer lupus anticoagulant antibodies are at higher risk for early rethrombosis. These patients are anticoagulated more aggressively. The choice of anticoagulant and target PTT varies. Choosing a therapeutic target can be particularly challenging in patients with significantly abnormal baseline PTT values.

Hypoxia is common following PTE. This is due largely to 2 phenomena: atelectasis and impaired ventilation-perfusion (V/Q) matching. Atelectasis is common secondary to prolonged surgery, splinting, and in some cases diaphragm dysfunction. V/Q mismatch occurs in areas of endarterectomized lung where autoregulation is disturbed. The lower resistance, endarterectomized vessels can “steal” blood flow from other areas of lung. It can take weeks to months before autoregulation is completely restored and perfusion imaging shows a more homogeneous distribution of blood flow (Figure 3). Hypoxia usually improves within 1-8 weeks following surgery.

PERSISTENT PH AND REPERFUSION PULMONARY EDEMA
The 2 postoperative complications that account for the majority of morbidity and mortality associated with PTE surgery are persistent PH and reperfusion pulmonary edema (RPE). They are often present in combination.

RPE is a syndrome that occurs following reinstitution of pulmonary blood flow to areas of lung that have undergone endarterectomy. It is defined by a PaO2/FiO2 ratio <300, opacity on chest radiograph in a region of reperfused lung with no alternative explanation such as pneumonia or atelectasis (Figure 4). Depending on the definition used, this is seen in 10% to 40% of patients following PTE.7-9 RPE is most common immediately following surgery (60%), with the remainder occurring in the first 48 hours following surgery (30%).10 A minority of RPE (10%) occurs >48 hours following PTE.

Standard approaches to the management of RPE include diuretics to reduce lung water and supportive care with oxygen and positive end expiratory...
pressure (PEEP). A single-center study examined the role of perioperative steroids to minimize RPE and found no difference between groups. In a study of 47 patients, a strategy of low tidal volume (≤8 mL/kg) and avoidance of inotropes and vasodilators has been suggested to reduce the incidence of RPE. Another study performed at UCSD examined the impact of different tidal volume strategies to reduce the incidence of RPE and did not demonstrate a difference. In the setting of severe RPE and elevated cardiac index (>3 L/min/m²) following PTE, cardiac output suppression with pressors may reduce capillary leak and lessen the severity of RPE. The effect of this strategy has not been prospectively studied.

In cases of persistent PH following PTE and/or hemodynamic impairment refractory to inotropic and pressor support, venoarterial extracorporeal membrane oxygenation (ECMO) (va-ECMO) has been used. In a report of 7 patients with persistent PH and hemodynamic instability at the time of PTE surgery, central va-ECMO was used as a salvage. Four of the 7 patients (57%) survived to hospital discharge.

In cases of severe RPE without hemodynamic instability, venovenous ECMO (vv-ECMO) can be used. The use of vv-ECMO for severe RPE was described in 20 out of 1790 (1.12%) cases over a 16-year period at UCSD. In this series, survival rates were lower in patients requiring vv-ECMO 30.0% vs 94.2%. Mortality was 100% for the 7 patients who initiated ECMO >120 hours after surgery. Based on these experiences, guidelines from the fifth World Symposium on Pulmonary Hypertension recommend that centers performing PTE have the capability of salvage ECMO therapy.

POSTOPERATIVE BLEEDING

The most common locations for postoperative bleeding complications to develop following PTE are the pericardium and the airway. Airway bleeding is usually observed immediately following PTE and can present significant management challenges. Pericardial bleeding can be observed early, while mediastinal drainage tubes are still present or late. Reported rates of pericardial bleeding complications have varied widely and occur in anywhere from 0.6% to 17% of patients. The development of late pericardial effusions following PTE has made echocardiogram following chest tube and pacemaker wire removal a routine part of postoperative care. Pericardial bleeding is managed in the standard fashion. Early bleeding requires return to the operating room for control of the bleeding site, and late effusions require temporarily holding anticoagulation and placement of pericardial drains.

Airway Bleeding Post-PTE Surgery

Airway bleeding following PTE can present significant challenges. Early diagnosis and prompt isolation of affected lung segments is essential. The surgeon is in a unique position to aid in this early diagnosis and management by anticipating airway bleeding. Suspicion should be high if the endarterectomy denuded the vessel and only a thin layer of adventitia remains or if a vascular injury was observed during PTE. In contrast, early acute severe reperfusion pulmonary edema should be suspected if the endarterectomy of a totally occluded vessel reveals a friable vascular bed. Isolation of the affected area will prevent blood spilling into other lung segments, which will preserve gas exchange in the unaffected lung.

Early diagnosis with bronchoscopy can set in motion actions that ensure the maintenance of adequate hemodynamics and gas exchange. A large injury is suspected if bronchoscopy identifies frank, dark, pulsatile blood in the airway upon weaning from bypass. Surgical repair or occlusion of that segmental pulmonary artery branch can be attempted. This repair or occlusion may require that cardiac and circulatory arrest be re instituted. In contrast, severe early reperfusion pulmonary edema is more likely if bronchoscopy reveals diffuse, pink, frothy material in the airways, and no attempt at vascular repair should be undertaken. The area should be isolated with a bronchial blocker followed by separation from cardiopulmonary bypass (CPB), reversal of heparin, and correction of coagulopathies. Effective isolation is critical to prevent blood from contaminating nonaffected lung and to successfully wean from CPB. Immediately prior to separation from CPB, the PCO₂ should be lowered and the PO₂ increased, as gas exchange may be suboptimal during the period when heparin is being reversed and coagulopathies corrected. If inadequate gas exchange persists, as evidenced by an ongoing drop in SpO₂, the bronchial blocker can be deflated, and if no bleeding is observed the isolated lung segment can be recruited for gas exchange.

Should inadequate gas exchange be an ongoing or recurring problem, vv-ECMO can be instituted; vv-ECMO without anticoagulation may be advantageous in the bleeding post-PTE patient by facilitating clot formation and allowing increased clot strength.
Ultimately aids in the resolution of airway bleeding. Even though some components of the ECMO circuit might not be heparin coated, we believe that the risk posed to the patient by ongoing airway bleeding outweighs the risk of clot formation in the cannula(s) or oxygenator. In fact, the oxygenator has a large reserve in function and will continue to supply adequate gas exchange despite some clot formation. Furthermore, clot(s) predominantly form on the inflow side of the oxygenator and therefore do not pose an embolic risk to the patient. If clot formation does impact oxygenator function, replacement of the oxygenator can be accomplished in a short time with little impact on gas exchange.

Arrhythmias

Arrhythmias are a common and expected complication following PTE. Functional arrhythmias dominate in the early postoperative period and atrial arrhythmias, in particular atrial fibrillation, can occur later. Epicardial pacing wires placed as a routine part of PTE surgery are removed once intrinsic cardiac conduction recovers.

Neurologic Complications

Neurologic disorders related to deep hypothermia have been observed following PTE surgery. The most common neurologic manifestation is delirium, which typically resolves with time.

The impact of PTE surgery on cognitive function was addressed by the PEACOG study performed in the United Kingdom. They examined cognitive function in patients undergoing PTE surgery and randomized 35 patients to traditional surgical technique with deep hypothermic circulatory arrest and compared them with 39 patients who received antegrade cerebral perfusion during PTE. While antegrade cerebral perfusion was safe, no differences in cognitive function were detected between the groups. Additionally, both groups showed improvement in cognitive function testing at 12 and 52 weeks after surgery. The improvement in cognitive function following PTE is speculated to be secondary to improvements in quality of life and oxygen delivery.

OUTCOME

Long-Term Survival

Long-term survival following PTE is excellent. For patients who survive to hospital discharge, survival rates of 92.5% at 5 years and 88.3% at 10 years have been reported in the United Kingdom. More recent data from the same center showed similar results with a 5-year survival rate of 90.0%. Other centers have demonstrated similar long-term survival results with reports from the Netherlands demonstrating 1-, 3-, and 5-year survival rates of 93.1%, 91.2%, and 88.7% respectively.

Functional and Hemodynamic Effects

PTE performed at experienced centers results in an immediate and sustained improvement in hemodynamics. The most recent series of patients published from UCSD resulted in a reduction of PVR from 719 ± 383.2 dyne·sec·cm⁻⁵ to 253.4 ± 148.6 dyne·sec·cm⁻⁵. Mean pulmonary arterial pressure improved from 45.5 ± 11 mm Hg to 26.0 ± 8.4 mm Hg, and cardiac output improved from 4.3 ± 1.4 L/min to 5.6 ± 1.4 L/min. Data published from CTEPH centers around the world have reported similar improvements in hemodynamics.

Most importantly, the improvement in hemodynamics is sustained on long-term follow-up. Data from the United Kingdom have shown sustained improvement in WHO functional class following PTE. Prior to PTE, 66% of patients were WHO functional class III or IV and 88% of patients had improved to WHO functional class I or II at 12 months following PTE. Mean improvement in 6-minute walk test following PTE of 103 ± 22.7 m was also sustained at 12-month follow-up. Data from Italy have shown similar results with a sustained functional improvement over a 4-year period, with 97% of patients NYHA III or IV prior to PTE and 74% improved to functional class I or II at 4-year follow-up. Other standard endpoints in the treatment of PH have shown sustained improvement following PTE. Patients from the Netherlands had sustained an improvement in NT-pro BNP following PTE from a mean of 1527 ng/L to 160 ng/L following PTE.

Persistent PH Following PTE

A uniform definition of persistent PH following PTE has not been established, and rates vary depending on the definition used. As previously mentioned, persistent PH and refractory right heart failure following PTE are some of the major contributors to early mortality. There are 2 distinct groups of patients with persistent PH following PTE: patients who achieve minimal or no hemodynamic improvement following PTE and patients who improve following PTE but continue to meet a hemodynamic definition of PH. For patients in the first group, early institution of advanced PH therapies including prostacyclins, endothelin antagonists, phosphodiesterase type 5 (PDE5) inhibitors and stimulators of guanylate cyclase, may be necessary as rescue. Consideration for lung transplantation in this group is appropriate. For the second group, consideration for additional medical therapy can usually be deferred until patients recover from surgery. Using a mean pulmonary arterial pressure ≥25 mm Hg or PVR >240 dyne·sec·cm⁻⁵ up to 35% of patients had persistent PH following PTE based on data from the United Kingdom. Despite meeting hemodynamic criteria for PH, 3-year survival for this group was 94% and 82% of patients remained functional class I or II.

CONCLUSION

PTE is and will remain the treatment of choice for CTEPH. Multiple factors are involved in determining candidacy for surgery, but no level of PH or degree of right heart failure is a contraindication to surgery. Excellent short- and long-term results can be achieved with adherence to established surgical principles.

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Medical Therapy for Chronic Thromboembolic Pulmonary Hypertension

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Chronic thromboembolic pulmonary hypertension (CTEPH) is caused by chronic organized thrombi obstructing the pulmonary vasculature. Thromboembolic obstruction of the pulmonary arteries leads to increased pulmonary vascular resistance (PVR), progressive pulmonary hypertension (PH), and right ventricular failure. Studies following patients who present with acute pulmonary emboli suggest that about 1% to 4% of patients develop chronic thromboemboli. In addition, about 25% of CTEPH patients never have an identifiable preceding acute pulmonary embolus. Therefore, the number of patients with CTEPH who will have persistent or recurrent PH after surgery, there is a set of patients with CTEPH that are not surgically accessible. In addition, there is a group of PAH patients that will not be operative candidates. Patients can have obstruction of subsegmental and more distal arteries that are not surgically accessible. In addition, there is a set of patients with CTEPH who will have persistent or recurrent PH despite successful PTE. Persistent PH is due to distal disease or arteriolar remodeling of unobstructed vessels, which cannot be corrected with surgery. Recently published data from an international registry of 679 newly diagnosed patients with CTEPH found that 37% of patients were considered inoperable. Nonoperability was mostly due to inaccessibility of disease (45%), followed by comorbidities and high PVR. It cannot be overemphasized that determination of operability requires great expertise and should only be made at centers that evaluate and treat many patients with CTEPH.

Rationale for Medical Therapy

Given the clinical and pathological similarities between CTEPH and PAH, there may be a benefit to using PAH-targeted therapies in this disease, specifically in nonoperable CTEPH or persistent PH after PTE. There is evidence that endothelin-1 (ET-1), a potent vasoconstrictor upregulated in...
PAH, is also elevated in CTEPH. Animal models of CTEPH have shown elevated ET-1 levels. In humans, ET-1 levels have been shown to be higher in patients with CTEPH when compared to healthy controls. ET-1 levels in 35 patients with CTEPH correlated with the clinical severity of disease and hemodynamic outcome after PTE. Patients with higher preoperative ET-1 levels had worse postoperative outcomes and were more likely to have persistent PH after PTE. Nitric oxide and prostacyclin pathways are also known to be important in the development of PAH. However, less is known about the significance of these mechanisms in CTEPH.

**Medical Therapy As a Bridge to Surgery**

Recent series of CTEPH patients undergoing PTE have reported in-hospital mortality rates of 2.2% to 5%. Risk of mortality seems to be related to preoperative hemodynamic severity, in particular an elevated PVR. A series of 275 patients who underwent PTE had a 4% mortality rate when PVR was less than 900 dynes/cm². Mortality increased to 10% when PVR was above 900 dynes/cm², and increased to 16.6% when PVR was greater than 1000 dynes/cm². Postoperative PH with a PVR greater than 500 dynes/cm² was associated with an even higher mortality of 10.3%. Whether surgical outcomes can be improved by refining preoperative hemodynamics with targeted PAH therapies remains unknown.

Small studies have aimed to answer the question regarding medical treatment prior to surgery. Treatment with intravenous (IV) epoprostenol in patients with CTEPH and severe PH (PVR >1000 dynes/cm²) was associated with preoperative improvements in PVR, mean pulmonary artery pressure (mPAP), and cardiac index. However, the impact on surgical morbidity or mortality could not be established from these small uncontrolled studies. Similar hemodynamic improvements were also seen in patients treated preoperatively with bosentan. Twenty-five CTEPH patients, candidates for PTE, were randomized to bosentan vs no bosentan. After 16 weeks of treatment, the bosentan group had significant improvements in mPAP, total pulmonary resistance (TPR), and 6-minute walk distance (6MWD). However, outcomes after surgery were similar in both groups.

Despite the lack of good data, the use of medical treatment prior to PTE has significantly increased in the past decade. A prospective analysis found that the use of disease-modifying PAH therapies had increased from 29% in 2001 to 65% in 2006. Another study reported an increase in medical treatment before PTE from 20% in 2005 to 37% in 2007. This high number was confirmed in the CTEPH registry, where up to 54% of patients were on at least one PAH-targeted therapy. A retrospective analysis of CTEPH patients referred for PTE compared 244 patients not on PAH therapy to 111 who were on therapy prior to surgery. The patients on medical therapy had a lower mPAP at the time of surgery. However, there were no significant differences in hemodynamic parameters, mortality, or complications after PTE between the 2 groups. The only significant difference was the time to referral for surgery. The median time to referral was 9 months in those on medical therapy vs 4 months in those without therapy. Therefore, preoperative medical therapy does not seem to improve outcomes and may lead to an unwarranted delay in surgery.

**Medical Therapy in Lieu of Surgery or After Surgery**

In patients deemed inoperable or with persistent or recurrent PH after PTE, several PAH-targeted agents have been evaluated, mostly in uncontrolled case series. Table 1 summarizes the studies of targeted PAH therapies in CTEPH.

**PROSTANOIDS**

There are limited data on medical treatment for inoperable CTEPH. A small, retrospective study showed that the use of the oral prostacyclin beraprost was associated with improved hemodynamics, functional class, and mortality in patients with CTEPH compared to retrospectively matched untreated controls. Treatment with IV epoprostenol in 11 inoperable CTEPH and 16 idiopathic PAH (IPAH) patients resulted in improved clinical status, exercise tolerance, and NYHA functional class after 12 months. Another retrospective study found improvement in hemodynamics and 6MWD after 3 and 20 months of IV epoprostenol in 27 patients with inoperable CTEPH. Only half of the patients had improvement in NYHA functional class. By the end of the study, only 9 patients remained on epoprostenol (5 got transplants and 13 patients died).

Inhaled and subcutaneous prostanooids have also been considered for treatment of inoperable CTEPH. A multicenter retrospective study examined the effects of subcutaneous treprostinil in 99 patients with IPAH and 23 patients with distal CTEPH. After 3 years, patients in both groups had significant improvement in 6MWD, dyspnea score, and NYHA functional class. Subsequently, an open-label case-control study of 25 patients with inoperable CTEPH or persistent PH after PTE found significant improvements in 6MWD, NYHA functional class, B-type brain natriuretic peptide (BNP) plasma levels, cardiac output, and PVR when treated with subcutaneous treprostinil. Survival was also better when compared to historical controls. Regarding inhaled prostacyclins, the Aerosolized Ilprost Randomized (AIR) study included 47 patients with CTEPH (23% total patients). A post-hoc analysis in this patient group found improvement in quality of life and dyspnea scores, without improvement in 6MWD.

**PHOSPHODIESTERASE TYPE 5 INHIBITORS**

A small, open-label study treated 12 patients with inoperable CTEPH and severe PH with sildenafil. Sildenafil was well tolerated and improved walk distance and PVR after 6 months. A larger open-label trial of 104 inoperable CTEPH patients found similar positive results after 1 year of treatment. This was followed by a single-center, double-blind, placebo-controlled pilot study that randomized 12 inoperable CTEPH patients to 12 weeks of sildenafil vs placebo. This was the first randomized
controlled trial ever done on CTEPH patients. The sildenafil group had improvements in NYHA functional class and PVR, but did not achieve the primary outcome of improvement in exercise capacity. This lack of improvement in 6MWD may be attributed to the study being under-powered. Based on these small trials, it

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Drug</th>
<th>Type of Study</th>
<th>Length of Study</th>
<th>Number of Patients</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olschewski et al, 2002</td>
<td>Inhaled iloprost</td>
<td>Multicenter randomized controlled trial (AIR)</td>
<td>12 weeks</td>
<td>101 iloprost (33 CTEPH), 102 placebo (24 CTEPH)</td>
<td>16.8% iloprost patients reached combined primary endpoint (improvement in NYHA class and at least 10% improvement in 6MWD) vs 4.9% in placebo group</td>
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<tr>
<td>Ono et al, 2003</td>
<td>Beraprost</td>
<td>Retrospective</td>
<td>2 months</td>
<td>20 beraprost, 23 matched controls</td>
<td>Improved NYHA in 50% of treated patients, Decrease in mPAP, Decrease in PVR, 15% mortality on beraprost, 70% mortality in controls</td>
</tr>
<tr>
<td>Scelsi et al, 2004</td>
<td>IV epoprostenol</td>
<td>Retrospective</td>
<td>12 Months</td>
<td>16 PAH, 11 inoperable CTEPH</td>
<td>Improved exercise capacity, Improved NYHA functional class</td>
</tr>
<tr>
<td>Cabrol et al, 2007</td>
<td>IV epoprostenol</td>
<td>Retrospective</td>
<td>3 months</td>
<td>27 NYHA III-IV</td>
<td>Increase in 6MWD, Decrease in mPAP, Increased cardiac index, Decreased TPR, 50% Improved NYHA</td>
</tr>
<tr>
<td>Lang et al, 2006</td>
<td>SQ treprostinil</td>
<td>Multicenter retrospective</td>
<td>26 months</td>
<td>99 PAH, 23 inoperable CTEPH</td>
<td>Increased 6MWD, Improvement in NYHA, Survival 89% 1 year, 71% 2 years</td>
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<tr>
<td>Skoro-Sajer et al, 2007</td>
<td>SQ treprostinil</td>
<td>Open-label case control</td>
<td>19 months</td>
<td>25</td>
<td>Increased 6MWD, 50% improved NYHA class, Improvement in BNP, Increase in cardiac output, Decrease in PVR</td>
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<tr>
<td>Ghofrani et al, 2003</td>
<td>Sildenafil</td>
<td>Open label</td>
<td>6 months</td>
<td>12</td>
<td>Decrease in PVR, Increase in cardiac index, Increase in 6MWD</td>
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<tr>
<td>Reichenberger et al, 2007</td>
<td>Sildenafil</td>
<td>Open label</td>
<td>1 Year</td>
<td>104</td>
<td>Decrease in PVR, Increase in 6MWD</td>
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<tr>
<td>Suntharalingam et al, 2007</td>
<td>Sildenafil</td>
<td>RCT</td>
<td>12 Weeks</td>
<td>8 sildenafil, 10 placebo</td>
<td>Improvement in NYHA class, Decrease in PVR, No significant change in 6MWD</td>
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<tr>
<td>Hoepfer et al, 2005</td>
<td>Bosentan</td>
<td>Open label</td>
<td>3 months</td>
<td>19</td>
<td>Decrease in PVR, Increase in 6MWD, No change in NYHA class or MVO2</td>
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<tr>
<td>Hughes et al, 2006</td>
<td>Bosentan</td>
<td>Open-label retrospective</td>
<td>1 year</td>
<td>47</td>
<td>Increase in 6MWD, Decrease in PVR</td>
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<tr>
<td>Jais et al, 2008</td>
<td>Bosentan</td>
<td>Multicenter RCT (BENEFIT)</td>
<td>16 weeks</td>
<td>77 bosentan, 80 placebo</td>
<td>Decrease in PVR, No change in 6MWD</td>
</tr>
<tr>
<td>Gofrani et al, 2013</td>
<td>Riociguat</td>
<td>Multicenter RCT (CHEST-1)</td>
<td>16 weeks</td>
<td>173 riociguat, 88 placebo</td>
<td>Increased 6MWD, Decrease in PVR, Improvement in NYHA class, Improvement in NT-proBNP</td>
</tr>
</tbody>
</table>
seems that sildenafil is well tolerated and leads to improvement in hemodynamics and functional class, without obvious improvement in exercise capacity. However, further larger studies would need to be conducted to better answer this question.

**ENDOTHELIN RECEPTOR ANTAGONISTS**

Several uncontrolled trials suggested that bosentan was not only safe, but may improve exercise capacity and hemodynamics in patients with inoperable CTEPH or persistent PH after PTE. An open-label safety study used bosentan for the treatment of 19 patients with inoperable CTEPH. After 3 months of treatment, patients had improvement in PVR and 6MWD, but no improvement in peak oxygen uptake or NYHA functional class. Similar results were seen in a subsequent small case series of 16 patients with inoperable CTEPH receiving bosentan for 6 months. A larger open-label retrospective study found that bosentan was well tolerated in 47 patients with inoperable CTEPH or PH after PTE. After 1 year of treatment there was improvement in 6MWD and hemodynamics, with no significant side effects.27

Given these positive findings, a large, multicenter, randomized, placebo-controlled trial was performed. The Bosentan Effects in Inoperable Forms of chronic Thromboembolic pulmonary hypertension (or BENEFIT) study, a 16-week randomized trial of bosentan therapy in 100 patients with CTEPH, was the first large randomized trial that looked exclusively at this patient population.28 One hundred fifty-seven patients with either inoperable CTEPH due to distal disease or PVR out of proportion to obstruction, or patients with persistent or recurrent PH more than 6 months after PTE, were randomized to bosentan or placebo. After 16 weeks of treatment, there was a statistically significant improvement in PVR (-24% of baseline) in the bosentan group. Despite improvements in PVR, there was no significant difference in exercise capacity. The reasons for this “disconnect” between the hemodynamic and exercise capacity effects of bosentan in the BENEFIT trial are not clear; patient selection may have played a role, as many patients were deemed “inoperable” due to other comorbidities and not necessarily anatomically inaccessible disease.

**RIOCIGUAT**

Riociguat is a member of a new class of drugs, soluble guanylate cyclase (sGC) stimulators. Riociguat acts both by enhancing the sensitivity of sGC to nitric oxide (NO), and as a direct sGC stimulator that will activate sGC to synthesize cyclic guanosine monophosphate (cGMP) in the absence of NO. Once sGC is activated, it converts guanosine triphosphate (GTP) to cGMP, which then leads to vasodilation.29,30 The Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase–Stimulator Trial (CHEST-1) was a large, multicenter, randomized, double-blind, placebo-controlled trial of 261 patients, randomized to riociguat vs placebo.29 Patients included had anatomically inoperable CTEPH or persistent or recurrent PH after undergoing PTE. After 16 weeks of treatment, 6MWD increased by a mean of 39 meters in the riociguat group, compared with a mean decrease of 6 meters in the placebo group (P<0.001) (Figure 1). There were also significant improvements in secondary endpoints, including hemodynamics. Pulmonary vascular resistance decreased by 226 dyne·s·cm⁻⁵ in the riociguat group, compared with an increase of 23 dyne·s·cm⁻⁵ in the placebo group. There was significant improvement in other hemodynamic variables in the riociguat group, including pulmonary artery pressure and cardiac output (see Table 2). Patients treated with riociguat also had improvement in NYHA functional class and reduction in NT-proBNP, when compared to placebo. Riociguat was recently approved in the United States for the treatment on inoperable CTEPH or persistent PH following PTE.

**SURGICAL VS MEDICAL THERAPY**

When thinking about medical therapy in CTEPH, early referral to a center of excellence with experience in pulmonary endarterectomy needs to be emphasized. Starting medical therapy should never delay referral for surgery. PTE has the potential to normalize hemodynamic and symptomatic impairments, whereas medical therapy cannot. Patients with operable disease have been found to have a 5-year survival of 90%,31 whereas inoperable patients have a 3-year survival of 70%.14,32 The decision to operate is dependent on whether the disease is surgically accessible, if the anatomic lesions “fit” the hemodynamics, and the severity of comorbidities. Currently there is no consensus or accepted algorithm to guide operability. This decision is based on center and surgical expertise.33

The international CTEPH registry found a large variation between countries and centers regarding the number of patients deemed operable.4 Low-volume centers reported up to 47% of patients evaluated as inoperable, whereas high-volume centers performing >50 PTEs a year reported 34% of patients inoperable. Therefore, more experienced centers may operate on cases others would deem inoperable. A recent large retrospective study from San Diego analyzed 1500 patients with symptomatic CTEPH who underwent pulmonary endarterectomy between 1999 and 2010.9 Despite having more distal disease, the most recent 500 patients had a comparable decrease in PVR and mPAP and an in-hospital mortality of 2.2%, compared to 5.2% in the first 1000 patients. Therefore, in an experienced center, the outcomes of
PTE are favorable even in patients with segmental level CTEPH.

**CONCLUSION**

CTEPH should be considered and ruled out in any patient with newly diagnosed PH. Clinically it can mimic PAH. It is important to distinguish between the two because the treatment strategies are different. The initial step in management of CTEPH should be referral to a specialized center with expertise in CTEPH, in order to assess operability. If PTE is successful, patients may return to normal or near-normal hemodynamics and exercise capacity after surgery. In those patients who are not surgical candidates or have recurrent or persistent PH after PTE, medical management with riociguat is appropriate.

**References**

**CTEPH Experiences and Expertise**

On February 6, 2014, a group of physicians with expertise related to Chronic Thromboembolic Pulmonary Hypertension (CTEPH) met on a conference call to discuss topics related to the disease. The call was hosted by the guest editor of this issue, Richard Channick, MD, the Director of the Pulmonary Hypertension and Thromboendarterectomy Program at Massachusetts General Hospital. Dr. Channick was joined by Victor Tapson, MD, Professor of Medicine in the Division of Pulmonary and Critical Care Medicine at Duke University Medical Center and Director of the Duke Pulmonary Vascular Disease Center; Joanna Pepke-Zaba, PhD, FRCP, Lead Physician and Director, National Pulmonary Vascular Diseases Unit at the Papworth Hospital, University of Cambridge, UK; Vallerie McLaughlin, MD, Professor of Internal Medicine at the University of Michigan; and Bill Auger, MD, Professor of Clinical Medicine and Director of Academic Affairs of the PTE Program at University of California-San Diego.

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**Dr Channick:** Welcome. We really appreciate your joining us from various time zones around the world. It's a pleasure to be joined by several distinguished colleagues to discuss the topic of CTEPH. I'm joined by Drs. Victor Tapson from Cedars-Sinai; Joanna Pepke-Zaba from Papworth Hospital in Cambridge, Vallerie McLaughlin from the University of Michigan, and Bill Auger at University of California, San Diego. We anticipate having quite a lively discussion. I will attempt to frame this topic in different sections and I'll ask each of you to take a section. As usual, we would like the discussion to be spontaneous and animated!

CTEPH is certainly topical given new therapies and our advancing knowledge about the treatment for this disease. But, of course, chronic thromboembolic disease starts with acute pulmonary embolism (PE). Vic, I know you've spent a lot of your career looking at diagnosis and treatment of acute VTE. What would you recommend in a patient who's had a large acute PE? Because presumably that's the patient who could go on to develop this CTEPH. What kind of follow up should these patients get?

**Dr Tapson:** Well, that's a great way to start, Rich. We don't have a lot of data supporting the fact that patients that have acute PE need repeat studies, such as repeat CT scans or echos. But I think one of the keys is those patients that come back to see us that haven't quite recovered. If somebody's still dyspeptic, they come back to see you in a month, a month-and-a-half, where most people with acute PE have recovered, those symptoms could be due to their underlying illness or represent persistent PE. The key is to look for persistent dyspnea, which is going to be the most common symptom. And when someone has those kinds of symptoms present, then further studies are warranted. A number of my colleagues might consider doing a CT scan in someone who had a big saddle embolism and recovered, just to make sure that has resolved completely. But we don't have a lot of data to support these kinds of tests, so a key is symptoms. Are there recurrent, persistent symptoms? And we certainly have to keep in mind that some patients may symptomatically improve or recover from an acute PE, but subsequently present with worsening symptoms and are found to have CTEPH. To follow patients after acute PE, we generally do a six minute walk test, where patients come back, kind of like we do in our pulmonary hypertension clinic. In addition to exercise capacity, we evaluate oxygenation. Because someone may come in, if they're a fairly sedentary person may not have a lot of evidence of persistent problem when, in fact, with exercise they may be hypoxemic. In addition, if the echo previously showed RV strain or PH, I would repeat an echo to make sure it has normalized.

**Dr Channick:** You mentioned an interesting phenomenon, which is patients becoming asymptomatic following acute PE and then going on to develop chronic disease. Bill, in San Diego, your group has described this as a “honeymoon period.” It seems like there is the risk of missing CTEPH in such cases if one is lulled into the false sense of security when patients are “asymptomatic” after 8 weeks. Do you agree?

**Dr Auger:** That's a really good point. And, yes, we have described this so-called honeymoon period, where after having experienced a large pulmonary embolism, the right heart compensates, even if the thrombus hasn't resolved completely and patients seem to do fine for a period of time. They seem to be doing fine and experiencing a normal course following their acute thromboembolic event on an antithrombotic therapy. And then months, if not years, down the road, they run into problems. The data are not strong enough to support that everybody should have a lung ventilation perfusion scan or echo every six months after they've experienced an acute pulmonary embolism. I agree with Vic, in that I think the evaluative process needs to be based on symptoms.

**Dr Tapson:** Another key time period is when you're considering stopping their anti-coagulation, whether it's 6 months or a year. If you're going to consider stopping it, another time point is to really make sure you know how the patient is feeling. And it may well be that a patient who is on continued anti-coagulation might have less of a chance of going on and getting CTEPH, although this is speculative.

**Dr Auger:** I agree with you, Vic.
Whether or not you keep people on anticoagulants is really a repetitive risk assessment at intervals following their acute event. Do they have a thrombo-philic state? Was the clot unprovoked? And so on. What are the ongoing risks that one individual has during their assessment dictates whether or not you need to continue their anticoagulants.

Dr Channick: One other area that gets debated is whether or not more aggressive treatment of massive or sub-massive PE, i.e., with thrombolysis, will decrease the likelihood of CTEPH. Maybe I'll ask Joanna, do you agree with that view? And at your center, are you more aggressive with the large acute PE in order to prevent CTEPH?

Dr Pepke-Zaba: We do not have much of the acute PE. But generally in the UK, we do not thrombolise unless the patient is hemodynamically unstable.

Dr Channick: Val, how about your center?

Dr McLaughlin: The same. And there are no strong data that thrombolysis is doing anything above anticoagulation. Vic, are you more aggressive about those with RV dysfunction?

Dr Tapson: Well, like Joanna said, I think really the data support lyrics for massive PE. The data don't even unequivocally support that approach. The expert opinion would support that, however. But for submassive PE in the groups we might consider, I think the data are still unclear. The PEITHO study should be published soon; it was presented last year and I think it should be published soon. They met the primary endpoint of decrease in hemodynamic deterioration in the PEITHO study, but we still don't have mortality data that prove thrombolitics improve mortality in our patients with submassive PE.

Dr Channick: It sounds like we can all agree that there really aren't good data that you're preventing CTEPH with more aggressive up front therapy. Which leads to the next topic, of course, which is why does CTEPH develop?

There are data that suggest it's not just the size of the initial thrombus. It's obviously a very complex disease. Joanna—tell us a little bit about why you think people develop CTEPH. Who gets it and why do you think they get it?

Dr Pepke-Zaba: I think that the problem is that there is no animal model of CTEPH disease. And this is why it's so difficult to talk about pathogenesis of disease to understand how the primary insult pulmonary embolism is not fully dispersed and is progressing to the chronic, rigid, and very variable obstruction of the vessel. We know that there are a number of medical risk factors that can contribute to development of chronic thromboembolic pulmonary hypertension. And this would be the history of cancer, thrombo-philic disorders, splenectomy. And there are some data suggestive of an inflammation associated to central catheters, such as pacemakers, wires, AV shunts. Blood groups other than O were also a predictor of CTEPH diagnosis and has been reported as a specific feature of the CTEPH patient population. How that affects clot resolution is again very interesting, but the data and our understanding of the pathobiology are limited. I think another interesting issue is how the clots are distributed in the pulmonary circulation. We know that the CTEPH is currently described as a two-compartmental disease of the proximal obstructions, which are suitable for the surgery—treatment of choice, and the distal obstructions are suitable for the surgery with pulmonary endarterectomy and/or secondary small vessel vasculopathy, where the medical treatment can be considered specifically now when potential medical therapy for inoperable CTEPH is available.

Dr Channick: This “two compartment” paradigm has always been very interesting to me. The number of pathophysiologic phenotypes in this condition are striking. For instance, we've all seen patients with very large clots and minimal “small vessel disease” and then vice-versa. Is it one disease with variable responses? Or are they really separate diseases? Bill, what do you think?

Dr Auger: The mechanism for developing CTEPH is still not entirely clear. I think there probably is a spectrum of pathology here. We've felt that in a large percentage of patients who ultimately develop CTEPH that the initial event is, in fact, an occlusive thrombus of the proximal pulmonary vascular bed with the secondary development of a downstream vasculopathy over a period of time. This gets us back to that whole concept of a “honeymoon period.” Perhaps the initial clot... which can often be a silent PE or wasn’t terribly symptomatic, provokes the gradual development of a secondary small vessel arteriopathy. This leads to the development of significant pulmonary hypertension, which becomes symptomatic. That certainly is one theory. Is it possible that folks develop a small vessel arteriopathy first with secondary thrombus development, as a different kind of phenotype for CTEPH? This might be a consideration... especially when you start talking about segmental level thrombotic disease. However, this theory is problematic and probably not the typical course of events in CTEPH patients. We still maintain that the initial event is that of a proximal vessel thrombus. This seems more logical when you consider that the endarterectomy surgery wouldn’t be beneficial if all you’re doing is taking out clot when the basic pathology is that of small vessel disease. But I think you’re absolutely right, Rich, when you speak of the wide range of clinical presentation in this disease. In some folks, it just seems to be the proximal vessel clot without much pulmonary hypertension, but they’re symptomatic from dead space ventilation issues. You take out the clot and everything gets better. In other patients, there’s really severe pulmonary hypertension and a limited clot burden. And so it really is a complex disorder.

Dr Channick: We’re certainly not going to discover the pathogenesis today, except to say it is complex. Just one last question on this topic: Do you think the clot grows in situ? Because the material removed at surgery often appears to extend down the branches over time.
Dr Pepke-Zaba: I think that it could. Just looking at what sort of lesions are on the CT scan, the complexity of the webs which are the residual after a previous insult, at least we understand that it can grow down peripherally. But that is rather our interpretation of the findings, not that we have proven it. Additionally, I just want to highlight that it has been shown that different distribution—more central or distal—of obstructions can affect right ventricle function. That might modify the individual person responses and the development of right heart failure contributing to the different phenotypes of CTEPH mentioned already by Dr Auger.

Dr Tapson: My suspicion would be that there has to be a genetic component or susceptibility. Bill could probably tell us his overall feeling about known thrombophilias and how often they occur with this disease. But it just seems to me there’s got to be a susceptibility factor, why some people get a clot and it doesn’t resolve like it should, assuming that’s the major pathophysiology.

Dr McLaughlin: We know, don’t we, Vic, that only about 20 percent of patients who have CTEPH actually have a known hypercoaguable state? There are likely many others that we haven’t identified.

Dr Tapson: Yeah, that’s absolutely right. I think there are probably thrombophilias we haven’t discovered or some genetic predisposition, or both, that make patients more susceptible. And as Bill has mentioned, many patients don’t have a history of VTE, maybe 50, 60 percent have a history of an acute event. And I think one thing we’ve found is that the more you talk to a patient, the more you come up with a previous event that sounds like it could have been PE—if they had a “pneumonia” three years ago, in the hospital for four days, and you talk to them about their pneumonia maybe they didn’t have that much cough or fever, which is kind of unusual with pneumonia. Or they had, a “cellulitis” in their leg two years ago, so the history does come out. But there must be some susceptibility factor here.

Dr Pepke-Zaba: One more thing: Genetic predisposition for the right ventricle to fail is very important, but that is completely different to the genetic predisposition for development of acute pulmonary embolism or CTEPH. So just for clarification, the most likely genetic factor will clearly distinguish the patient with the chronic thromboembolic pulmonary hypertension, a very rare disease, from those who are developing acute pulmonary embolism, which is common. So we are potentially talking about two completely different genetic diseases.

Dr Channick: Which leads to a very important question: What, in fact is the true incidence of CTEPH? In the literature, we read numbers ranging from less than 1 percent to 4 to 7 percent.

Dr Pepke-Zaba: Well, I think that we don’t know. (laughter) I can only tell you that the number of patients with chronic thromboembolic pulmonary hypertension in the UK has grown dramatically since we have started the national program. And now, CTEPH is the second biggest subgroup of the patient with pulmonary hypertension that’s seen in the pulmonary hypertension centers in the UK.

Dr McLaughlin: Well, it’s one of those things, the more you look for it, the more you’re going to find. Sadly, a lot of people don’t look for it.

Dr Pepke-Zaba: And we are trying to retrospectively look into the CTEPH population and find out how many — how it relates to the acute PE in the region. But it’s very difficult because there are no good data that can estimate acute pulmonary embolism.

Dr Tapson: Yeah, the Pengo data are interesting. You remember that study, of course, in New England Journal, probably ten years ago. They had a couple hundred patients. And these patients had a first PE, so they had to have a documented event to be included in this study. They were followed after their acute event and ultimately had a rate of about 3 or 4 percent of CTEPH. But those were patients who had a documented event. So it may be higher than we think and I bet a lot of our colleagues out there and maybe ourselves have patients we follow for PH that may still have unrecognized CTEPH.

Dr Channick: Another limitation of that study was that pulmonary hypertension was diagnosed only by echo.

Dr Tapson: Yeah, that’s a good point. So it may have overestimated it.

Dr Channick: Bill, you can attest to the phenomenon that fellows who trained at UCSD start “epidemics” of CTEPH when they’d go out after their training!

Dr Auger: Val makes a really good point. You’re not going to make the diagnosis unless you look for it. The experience has always been that when people really start thinking about the possibility of CTEPH, that’s when they start picking it up. Studies that attempt to look at the incidence of CTEPH typically follow patients after an acute thromboembolic event or a recurrent thromboembolic event. Unfortunately, there are a number of folks with pulmonary embolic events who don’t present symptomatically. So there is a hard-to-define group of patients out there with previously unrecognized PE that ultimately come to you with dyspnea for unclear reasons. It’s in these patients particularly, unless you think about the diagnosis of CTEPH and screen for it, you’re going to miss it.

Dr Channick: Okay. So if every case of CTEPH was diagnosed that exists in the US, how many surgeries would there be per year? (laughter). For the sake of discussion, we are assuming that all got referred to a center where they had surgery. What would be the number? Five hundred, a thousand, ten thousand?

Dr Pepke-Zaba: The UK population is 64 million. We have performed 153 pulmonary endarterectomies in the last year, previously 150 operations, and we still have a waiting list for the surgery.

Dr Tapson: I think part of the answer to that question lies in the fact that after
starting to see these patients and spending a little time reading CT scans with Bill Auger, that this is an art, reading these CT scans. And I’m convinced, if you’re not thinking about it, like you guys have said, you’re going to miss it. And even if you’re a good radiologist, you can still miss it if you don’t see this disease a lot. You may not see the subtle findings. We’re not looking for intravascular defects, like acute PE, we’re looking for abnormal vessels that have been remodeled and are unusual looking. And boy, I’ll tell you, you guys who have spent time at San Diego have seen a lot of these, and it’s an art.

Dr Channick: Yes, no about that! So what’s the number?

Dr Auger: We just don’t know how many endarterectomy surgeries are performed, or how many potential surgical candidates there are in the US. Our best guess is based on what limited surveys we have. Given the small number of specialized centers around the United States, there’s probably about 400 thromboendarterectomies being done each year. But that is purely speculative. . .and assuming that all cases of CTEPH correctly identified as operable are having surgery. Which leads to the larger question of how many patients there are with newly diagnosed CTEPH who are not deemed to be surgical candidates for one reason or another. We just don’t know.

Dr Channick: So if you are correct regarding 400 PTEs per year in the US, given the number of people surviving PE per year, that would correlate to approximately a 0.1 percent incidence which would be at the low end of the incidence or prevalence estimates.

Dr Auger: What do you think about that, Val, as far as the number of cases?

Dr McLaughlin: The number of cases currently being done? I mean, you guys alone do what, 300 a year?

Dr Auger: No, we did 162 cases in 2013, so, maybe near half of the cases in the United States, I would imagine.

Dr McLaughlin: So that 400 may be a little high, actually. There’s you guys’, obviously you’re the world’s leading most experienced center in it. And then there’s a modest number of centers that do a modest number of cases. So, I think probably the rest of us combined, maybe we come close to what you do. So I think it’s probably less than 400.

Dr Channick: So suffice it to say that we’re probably not doing nearly as many PTEs in the US as there are operable patients.

Dr McLaughlin: That’s exactly the point. I mean, you know, whether it’s 300 or 400, it’s still a lot less than what you would expect, based on the epidemiology of the disease.

Dr Channick: Right. Which gets me to the next topic. Val, as someone who has a very large pulmonary hypertension program, how do you do an initial evaluation for CTEPH and at what point do you decide to refer a patient for consideration of surgery? And what is the testing that you do as opposed to allowing the referral center to do?

Dr McLaughlin: With regard to diagnostic testing, I think we’ve all been involved in discussions, talking about the importance of ventilation/perfusion scan as the study of choice to screen in a patient who has unexplained dyspnea and pulmonary hypertension. While Vic has outlined some of the very nice changes that you see on spiral CT scan, they are sometimes difficult to interpret. You can sometimes miss surgically accessible disease. So the V/Q scan is the screening test of choice. Often, patients will come to us with a spiral CT and we would generally repeat a V/Q scan. There may be a case here or there— and I would love Vic or Bill’s opinion on this— for instance a scleroderma patient who has some interstitial lung disease, in whom you think the V/Q’s not going to be all that helpful, that maybe we’ll look more closely at the CT. But one of the key factors is doing the ventilation/perfusion scan. Unfortunately, this is a practice that is not followed as much as we would like to see. In fact, in one of the registry studies that have been done over the past few years, we see that about half of the patients who ultimately get diagnosed with group 1 PAH do not have a ventilation perfusion scan. Hopefully CTEPH is being evaluated in some other way, but they’re not getting the study of choice. Once a patient has a suspicion of chronic thromboembolic disease as we’re working them up, be it a patient without a history of PE who has an abnormal V/Q or someone that comes with that history, certainly the pulmonary angiogram is the roadmap. And, at our center, we feel comfortable doing the right heart caths and pulmonary angiograms in these patients. We have enjoyed a wonderful relationship with UCSD over the years. I’ve sent them many patients over the years and they’ve been great about initially looking at the films and the records, to see if it’s worth a trip. Over the most recent years, we have started doing some thromboendarterectomies at our center. UCSD was gracious enough to host one of our surgeons and some anesthesiologists. As a newer center, you obviously have to pick your initial cases very carefully. And so we’ve worked together with our surgeon, anesthesiologist, and also with UCSD to help select the appropriate cases for a newer center to do and we’ve had success, but we still work with UCSD for a lot of these patients.

Dr Channick: Thanks. Bill, I know you get patients referred at all stages of evaluation. Can you add anything to that? I’m sure you’re willing to review the V/Q scan or do everything at the center? How do you interact with the referring doctors in this regard?

Dr Auger: Val has appropriately emphasized the need in patients with known pulmonary hypertension to take a closer look at the pulmonary vascular bed, and the recommended screening study for CTEPH would be a perfusion scan. And simply put, the perfusion scan will be either normal or abnormal. If it’s normal or showing just kind of a grainy pattern of hypoperfusion, then the chance that that patient will have surgical or operable CTEPH is virtually
zero. If it’s abnormal, then the diagnosti-
cian needs to move forward and
evaluate the pulmonary vascular bed in
some other way. Although with appro-
priate precautions, conventional
pulmonary angiography can be safely
performed in pulmonary hypertensive
patients, and can provide a tremendous
amount of information as to whether a
patient has operable CTEPH; it is
becoming a lost art. Evolving technology
is such that examining the pulmonary
vascular bed with CT and/or MR . . .
and particularly with CT . . . is an
increasingly valuable diagnostic tool as
long as it’s interpreted appropriately.
Everyone here can appreciate that even
patients with extensive small vessel
disease can have an abnormal perfusion
scan. So an abnormal perfusion scan, in
and of itself, is not enough to say that
somebody has surgical CTEPH. You
just need to image the pulmonary vas-
cular bed in another way, be it with
conventional pulmonary angiography,
CT, and/or MR.

Dr Tapson: Bill, can I ask you a
question. Given the availability of really
good CT scans, do you still feel it’s ne-
necessary to do a PA gram in all patients?

Dr Auger: Really, it depends on the
circumstance. We have observed
numerous cases where the CT
angiogram has clearly understated the
amount of chronic thromboembolic
disease present. As surgical techniques
have been advanced, particularly both at
Papworth as well as at UCSD, where
segmental level resection is not only pos-
sible, but hemodynamically beneficial, it
becomes increasingly important to define
operable CTEPH in a region of the vas-
cular bed where CT can sometimes
understate the extent of disease. So, par-
ticularly in those individuals in whom
we’re still unsure whether or not they
have operable chronic thromboembolic
disease, we will do conventional angiog-
raphy. But in some circumstances where
hemodynamic data are available, and we
know how sick those patients are, and
CT angiography demonstrates a lot of
proximal chronic thromboembolic
disease, conventional pulmonary angiog-
raphy is not necessary.

Dr Tapson: Maybe I could just
mention one additional aspect of diag-
nosis, based on something Val
mentioned. We do have two sclerodera
patients that went through our usual
pulmonary hypertension workup when
they presented with progressive dyspnea.
And we did their V/Q scan, as we
always do, and both had high probability
scans, had CTEPH, and both have been
operated on now. So even if we have a
known other cause of pulmonary hyper-
tension, the patient still might have
CTEPH.

Dr Channick: I agree. Although our
experience has demonstrated the impor-
tance of the V/Q scan—and I would
certainly classify myself as a “believer”–
that belief is not held everywhere.
Joanna, at your institution in the UK,
are perfusion scans still performed rou-
tinely? I know at some European centers
they’re not as readily utilized.

Dr Pepke-Zaba: No. CT scanning is
much more popular than V/Q in the
UK generally. Usually, the patient will
have a CT scan and if CT scan suggests
some degree of pulmonary occlusions,
the patient might go to the V/Q scan to
look for the sort of wedges which have
been already mentioned. And we do like
to see perfusion scans with those nice
wedges before the surgery. But we also
like MRI angiography. And this is a
much better way of imaging proximal
pulmonary vasculature compared to the
CT scan. I totally agree that CT can
often underestimate the disease burden
and our surgeons like MRI.

Dr Channick: So MRI is typically your
confirmatory test?

Dr Pepke-Zaba: Yes.

Dr Tapson: One thing I’d say about
MRI, I think you’ve got a clinician like
Joanna, in a center like they have, it’s
probably a great option. We learned in
PIOPED 3, at least for acute PE, that
the interpretation of MR really depends
on the radiologists reviewing them. I’m
sure that would probably hold for
CTEPH even more, since it’s a difficult
diagnosis.

Dr Channick: Let’s move on to the
next topic: surgery—and I’ll turn to Bill,
to take us through the referral process
and the typical course once the patient
gets referred to your center. And then a
little bit about the really impressive out-
comes after surgery.

Dr Auger: We certainly are available
to do as much of the preliminary work in
evaluating patients for possible surgery,
evem prior to their traveling to San
Diego. The first step is a request for
certain studies that might indicate the
patient might have CTEPH, such as an
abnormal lung ventilation perfusion scan
in the setting of pulmonary hyper-
tension. With an abnormal perfusion
scan, a request will go out either for a
CT or other imaging modalities to better
define what those perfusion abnormal-
ities might be from. Most clinical
centers—unles you’re coming from a
fairly large medical center—don’t typically
perform conventional angiography in
pulmonary hypertensive patients and
hence our increasing reliance on CT
angiography in order to prescreen
patients for possible operative chronic
thromboembolic disease. And once it
seems that this person is a potential can-
didate for surgery and it is apparent
there’s the desire on the patient’s part to
pursue a surgical option.

Dr Channick: Let me just stop you
real quick right there. So let’s say I’m a
referring physician, and I call and say, “I
have this guy. He’s in his late 70s. He
has some coronary disease.” Is he really a
candidate for this operation?

Dr Auger: Available data would
indicate that age in and of itself is not
an exclusion criteria for undergoing end-
arterectomy surgery. We’ve operated on
patients as old as 88 at UCSD.

Dr Pepke-Zaba: You have beaten us.
Our current is 86.

Dr Tapson: It’s really remarkable. Of
course, these folks have a tendency to
select themselves out as being fairly
hearty in the first place. To Rich’s point,
is there an age cutoff? And certainly,
what affects perioperative mortality risk
is not so much age but the comorbidities that come with somebody's age. And this particular person at 88 had very few comorbidities that would adversely affect his perioperative course.

**Dr Channick:** I think it is very important to stress to the readers of this roundtable, some of who may not have diagnosed CTEPH or referred patients for PTE surgery, that this procedure is not “experimental” and has been performed for decades. At large centers of expertise, it is considered almost routine. The postoperative course can be very straightforward, with great outcomes; PTE is a truly lifesaving and life changing procedure. Even at my institution, MGH, when I started the CTEPH program 4 years ago, my esteemed colleagues really didn’t have an appreciation for the procedure and its benefits. Now that we are regularly performing the procedure, everyone is a believer! Joanna and Bill, you both have very large programs. Can you elaborate?

**Dr Pepke-Zaba:** I think the most important is to highlight that mortality now has been dramatically reduced. And in the cases without specific comorbidities, is within the sort of range of any other major cardiac surgery. So we are talking about 2 percent or under 2 percent mortality for the simple cases. I think that’s very important to highlight. However, the learning curve at the beginning is very, very steep. The long-term outcomes after the patient recovers from the surgery are excellent. Perioperatively, our average stay on the ICU is 48 hours, patients are walking out from the hospital within 18 days. After 3 months practically, they are back to normal functioning. And good functional status is further improved or maintained for a long time. We’ve got follow up data with the hemodynamics up to 1 year. And the patients are observed routinely in other PH centers for 5 years-plus. We are currently putting long-term data together, but the mortality of the patients who are surviving the surgery is very good and 5 years’ survival is about 95%, which is equal to the one which you expect in this age group, which is around 60-plus.

**Dr Auger:** And Rich, we’re experiencing the same thing. I can underscore that as your experience grows, your mortality rates drop. Over the last five years, we are seeing an overall perioperative mortality of less than 2 percent for our patients, with very little impact now on the level of acuity and/or the severity of the pulmonary hypertension preoperatively. Our median time on the ventilator is a day. Our median time in the ICU is 3 days now. And our median length of stay postoperatively is down to 10 days. But that just comes with doing a greater number of cases. And I think every center that performs this particular operation shares this same experience.

**Dr McLaughlin:** Absolutely! There is no question that the outstanding outcomes that we see are due to the multidisciplinary team approach to CTEPH. An experienced medical diagnostician who can interpret imaging and hemodynamics to choose acceptable surgical candidates, an experienced surgeon, and good postoperative care are all critical to success.

**Dr Channick:** Absolutely! Joanna and Bill, you both have very large programs. Can you elaborate?

**Dr McLaughlin:** I think that’s true, Bill. But I think the other thing to maybe point out is just patient selection, too. I mean, not all CTEPH is operable. And not all CTEPH that you see is proportionate to the amount of pulmonary hypertension. And so some of those things go into selecting appropriate patients for the surgery.

**Dr Auger:** Rich, I’m waiting for you to ask the next provocative question. What constitutes operable CTEPH? Because Val is absolutely right, not every patient with CTEPH is a candidate for the surgery. This is an exciting time in the world of CTEPH with advancements in surgical techniques, and the availability of medical therapies for patients with nonsurgical CTEPH.

**Dr Channick:** I hesitate to delve into what constitutes operability, because this is a complicated decision that requires extensive experience, something you can’t explain in sound bites. Being able to interpret the PA grams in the context of the pulmonary hemodynamics, patient symptoms and comorbidities, is a skill that only comes with time. But suffice it to say that there will be some patients deemed inoperable. Which gets me to the last topic: What is the role of medical therapy? Val, you’ve been involved in helping develop many of our approved, highly effective medical therapies for pulmonary arterial hypertension. What is the role of medication in CTEPH patients? This question is especially relevant since there is now a medication approved for inoperable CTEPH or post PTE residual pulmonary hypertension.

**Dr McLaughlin:** Right. So that’s a good question, Rich, and Bill, yes, it’s an exciting time. I just want to emphasize one thing before we go onto this. That is that every patient deserves the benefit of the doubt and deserves to be at least looked at for surgical evaluation. We’re not going to get into the nitty-gritty of what makes a patient operable or what doesn’t. But everybody at least deserves an operability assessment, whether there’s a center locally, whether you send films to UCSD, or someplace else. The last thing we want to do is give a medical therapy to someone who could be essentially cured or very well treated with a surgery. So we really need to highlight that, despite all the enthusiasm about the medical therapies that we have. One of the things that may happen to some of these patients is that they have very distal disease and we can’t get to it or they develop what we’ve referred to as a small vessel arteriopathy and they act much more like a pulmonary arterial hypertension, even though they have some amount of distal clot burden. For years, we have occasionally extrapolated PAH therapies to those patients who weren’t surgical candidates, just because we had nothing else to offer them. And there are some case reports of that helping and I’m sure we all have experience of patients who had some improvement in their symptoms on PAH-specific therapies. Rich is alluding to the recently approved soluble guanylate cyclase stimulator, riociguat, which has been studied in two randomized controlled trials. One was in Group 1 PAH and the other in patients with chronic thrombo-
embolic disease that was either not surgical. There was a very intensive surgical operability assessment for those patients, so they were deemed not operable, primarily because of distal disease that was not surgically accessible, or if they had persistent pulmonary hypertension, after an endarterectomy that had occurred at least, I believe, about six months previously. Those patients were randomized to either riociguat or a placebo and followed for a period of 16 weeks. There was an improvement in the primary endpoint of six minute hall walk and some secondary endpoints, including hemodynamics, in those patients. This is really the first good randomized control data of a medical therapy being effective for patients with chronic thromboembolic disease. So there is another option to offer these patients who are not surgical at this point. It’s a bit of a complicated drug to use. It has side effects, as all drugs do. It needs to be titrated. One needs to monitor blood pressure. But for those particular patients, it can be an effective means of treating their symptoms of dyspnea and exercise intolerance.

Dr Tapson: I think it’s exciting now to have a therapy we can use in those patients who are not operable or who do have problems after surgery. I know we’ve stressed this point already, but I want to underscore that before using this medication, we’ve got to make sure that the patient is not a surgical candidate.

Dr Channick: I agree. However, in reality, patients are often placed on medical therapies either in lieu of, or prior to surgery. Bill, you’ve published on the role of medical therapy prior to PTE and the potential for delaying referrals for definitive treatment.

Dr Auger: Yes, there’s that concern. Currently nearly 50% of the patients who come to UCSD who ultimately undergo surgery are on PH medical therapy. So I just suggest that clinicians resist the temptation... if it’s truly operable disease, the patient’s pulmonary hemodynamics are relatively stable and there are no signs of RV failure, to avoid unnecessary medical therapy. I know that there are a lot of things that need to be considered prior to patients’ having surgery... we don’t have the data that say that medical therapy is a good thing to prep patients before a PTE. However, if you have a patient with unstable hemodynamics, treatment of RV dysfunction while awaiting surgery is appropriate, and the referring doctor should work with the center that’s going to be doing the operation.

Dr Pepke-Zaba: I think that what probably is happening is that the patients who are treated with a medical therapy are much more complex with more co-morbidities and are much more hemodynamically unstable. Some time ago there was a simple work project looking into removed specimens from the patients on different bridging therapies. Obviously, it’s very difficult to compare stiffness, elasticity, compliance of the specimens because we can’t apply force to measure it, but there were no obvious differences between the samples assessed by experienced pathologists.

Dr Auger: We’re also looking into that, Joanna. There is the sense from our surgeons that perhaps there is a change in the texture of the clot, making it more difficult to remove. A successful endarterectomy is based on adequately creating a dissection plane, such that this chronic, organized, fibrotic-type material can be removed from within the pulmonary vascular bed. The key to a successful operation is removing as much of the clot as possible. If that’s more difficult, then the surgeons are in the pulmonary vascular bed a longer period of time. That doesn’t mean that it becomes an unsuccessful operation; it’s just a more difficult operation. But one is challenged when you’re on the phone with referring doctors and they have a patient who is very, very sick, with significant pulmonary hypertension, and very symptomatic. Doctors want to be able to do something for their patients while they’re awaiting their surgery... what do you do in that setting when you know these drugs haven’t been studied for this particular indication?

Dr Channick: In some ways, I’m even more worried about patients at the other end of the spectrum, maybe a little less sick, where physicians may say: “Let’s give this medication a try and see how you do for six months or a year before we consider referral for surgery. We’ve all seen that scenario. In somebody with operable disease who maybe is not as advanced, maybe it’s not a good idea to wait. Maybe we’re risking more progressive arteriopathy that will be less amenable to surgery.

Dr McLaughlin: And what about more RV dysfunction over time? For these reasons, I would discourage the “wait and see” approach. The cases for whom we’ve used preoperative medical therapy, as Bill alluded to, are those patients that are really sick, have a lot of RV dysfunction, that we’ve gotten a bit aggressive with—more to try and improve their hemodynamics, the function of their RV—before a surgery. I would agree that treating someone with a medical therapy just to see how they do, when they have operable disease and could essentially be cured by a surgery is probably not what we should be advocating.

Dr Auger: I don’t want my statements to be misconstrued that I’m advocating medical therapy prior to surgery, because Val, you’re absolutely right. CTEPH patients with clearly operable disease, outcomes following surgery are far superior compared to medical. You’re really not achieving much by putting patients with significant pulmonary hypertension due to chronic thromboembolic disease on a PH medication when the best chance for a cure is surgery.

Dr Channick: Thanks Bill. Well, time is up, so I think we’ll stop there. It’s certainly been a pleasure and we’ve had a great interactive discussion of this important topic. Thank you, everybody.
Pulmonary thromboendarterectomy (PTE) surgery has revolutionized the treatment of chronic thromboembolic pulmonary hypertension (CTEPH). The majority of patients who undergo PTE report good functional status and improved quality of life, and survival of patients who undergo PTE is considerably greater than patients who have not undergone surgery. However, despite its significant benefit to patients, providers caring for these patients postoperatively must be aware of a number of clinical sequelae of the procedure. The purpose of this article is to present an overview of what to expect during the first year following PTE surgery. Postoperative hypoxemia, post-sternotomy limitations, pericardial effusion, long-term anticoagulation, and residual pulmonary hypertension (PH) are issues that arise and will be addressed.

It is very common for patients to manifest post-procedural hypoxemia, which may persist for months. Even patients who did not require supplemental oxygen prior to PTE may need oxygen for several months following their procedure. The mechanism of this hypoxemia is believed to originate from ventilation-perfusion mismatching, which commonly occurs from a variety of causes. Pulmonary vascular “steal” is a phenomenon uniquely seen in a great deal of PTE patients and results from reversible redistribution of pulmonary blood flow away from previously well-perfused lung regions into newly endarterectomized segments induced by the surgery. This redistribution of flow can give the postoperative nuclear perfusion scan a very abnormal appearance that tends to improve over the following year. For this reason, a follow-up ventilation/perfusion scan is suggested 6 and 12 months following PTE surgery to establish a new baseline for the patient. As with other cardiothoracic surgical procedures, postoperative atelectasis can also contribute to hypoxemia, as well as hemidiaphragm paralysis due to phrenic nerve injury related to the procedure. Periodically assessing the patient’s oxygen saturation following surgery is advised so that supplemental oxygen can be weaned and discontinued as oxygenation improves.

As with any procedure that requires a median sternotomy, patients may be limited by postoperative pain. Patients exhibit a wide variety of perceptions of pain, with many requiring narcotics for several weeks following discharge to those who are easily managed with acetaminophen. Patients with chronic pain syndromes prior to surgery can be particularly challenging to manage in the postoperative period given their tolerance to narcotics. A pain specialist may best manage such patients after discharge. Current guidelines for sternal precautions recommend that patients should avoid lifting more than 5 to 10 pounds, weight bearing of the upper extremities, driving, or returning to work for 6 to 8 weeks to reduce the risk of sternal complications. Certain risk factors are associated with sternal wound complications including obesity, diabetes mellitus, redo sternotomy, COPD, smoking, and female gender with large breast size. It is therefore important for patients to adhere to these short-term activity limitations. Any signs or symptoms suggestive of sternal wound infection such as increased redness or drainage from the incision, fever, or sternal instability should be evaluated immediately as these infections can be life threatening if not dealt with promptly.

The importance of lifelong anticoagulation should be stressed in this patient population, which has a strong propensity for rethrombosis. Unless contraindicated, warfarin is typically recommended after PTE, as its effects can be measured and reversed in the event of a hemorrhagic complication. The role of newer oral anticoagulants in the treatment of patients following PTE surgery has yet to be determined. The provider has to be vigilant for any of the known complications related to anticoagulation.

Pericardial effusion may occur after PTE, in part due to the early use of anticoagulation and the complexity of the surgery. Pericardial effusion most often develops within the first month following PTE. Common symptoms include acute dyspnea, malaise, chest pain, presyncope, or syncope. Clinical features of tamponade may include hypotension, tachycardia, and pulsus paradoxus. When pericardial effusion is suspected, it is imperative the provider promptly obtain an echocardiogram and chest x-ray. A chest x-ray is easy to obtain quickly and may demonstrate an enlargement of the cardiac silhouette, but echocardiography is the definitive study in diagnosing pericardial effusion. Management strategy depends on the patient’s clinical condition and echocardiographic findings.

For smaller effusions, holding anticoagulation short term and/or steroids or colchicine may be effective in resolution of the effusion. For larger effusions,
especially with tamponade physiology, evacuation is necessary. Patients should continue to exhibit clinical improvement following PTE surgery. Any clinical deterioration such as worsening of dyspnea, chest pain, hypoxemia, or evidence of right heart failure or hemodynamic instability should prompt the provider to order an echocardiogram immediately since tamponade is life threatening. Postoperative pleuritis/pleural effusions may also be seen and are managed similarly to pleural effusions following other cardiothoracic surgical procedures with observation, drainage, or steroids, depending on the size and symptoms.

Finally, post-procedural residual PH can be observed in some cases. The pathogenesis of such residual PH may be related to the inability to surgically resect all of the thrombus/fibrotic material from the pulmonary arteries during the procedure or superimposed small vessel vasculopathy that is similar in appearance pathologically to PAH. PAH-directed medical therapy may have a role in the treatment of these patients. There are no guidelines that define what level of residual PH following PTE surgery should be treated or when therapy should be initiated. However, prior to committing to this costly and arduous journey, patients should consult a center with expertise in CTEPH.

In summary, while the majority of CTEPH patients experience improvement in right heart function and symptom relief after PTE, the recovery period can be overwhelming for many. It is important to note that many patients do not have such issues after surgery. Knowing what to expect during the first year after PTE offers peace of mind for patients and clinicians alike.

References
ASK THE EXPERT

Do Patients With Pulmonary Arterial Hypertension Benefit From Referral to a Specialized Center?

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Expert medical specialty care in the modern era took shape in the 19th century, according to an analysis by George Weisz,1 as a result of clinical researchers seeking to “permit rigorous observation of many cases” of similar illnesses and to best manage illness at the population level. The development of medical specialties, and more recently subspecialties, provides a general endorsement of the concept that appropriate use of specialized care is beneficial. For a rare/orphan disease such as pulmonary arterial hypertension (PAH),2,3 the opportunity to improve care through specialized centers may be even greater since direct patient care experience outside such centers is uncommon. To justify the potential downsides including increased medical visit burden, traveling longer distance to the specialty center, and possible added costs, significant benefits of care at expert centers should be expected. To best support the argument for referral, this anticipated benefit should be evidence-based, include independent accreditation of specialty centers, and offer multiple opportunities to improve outcome and quality of life in PAH.

The fifth World Symposium on Pulmonary Hypertension (WSPH) recommends expert/specialized center referral with a 1-C grade, meaning that: “Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, or effective based on consensus of opinion of the experts and/or small studies, retrospective studies, registries.”4 The authors based this recommendation on the observed success of the specialty center model for PAH care that has evolved in many countries,5 potentially improved access to possible emergency PAH treatments,6 and benefits of “high-volume specialized centers [that] have been recurrently shown to obtain the best outcomes for patients in different areas of medicine while maintaining greatest patient satisfaction, lowest complication rates, shortest length of hospital stay, and best value for health care payers.”7 The history of surgical therapy for chronic thromboembolic pulmonary hypertension (CTEPH) has also supported the concept of improved outcomes from high-volume centers: operative mortality has declined as centers gained greater experience through higher procedure volume.8,9

Consistent with the WSPH recommendations regarding expert/specialty center referral, the Pulmonary Hypertension Association (PHA), through its Scientific Leadership Council, has developed a pioneering program, the PHA-Accredited Pulmonary Hypertension Care Centers (PHCC) initiative. This accreditation program has as its ultimate mission the improvement in outcomes for patients with PH. In addition, the PHCC program is intended to provide education that ensures best practice based on guidelines, to facilitate the establishment of care registries, and to promote further clinical research. In their editorial published elsewhere in this issue,10 Chakinala and McGoon describe these efforts in detail from the PHCC Committee. These authors mention the impact of published study data such as that from the RePHerral Study, the PAH-QuERI project, and the REVEAL Registry, which suggest instances of diagnostic inaccuracy, underutilized guideline-based testing, and failure to prescribe parenteral prostacyclins ever or in a timely manner in patients with advanced disease. These gaps in PAH care present

Table 1. Potential advantages of referral to and collaboration with an expert specialty center for PAH

| • Confirmation of diagnosis, especially in complex cases |
| • Initiation of treatment as early as possible |
| • Monitor therapy for adequacy of response |
| • Manage medication side effects |
| • Change or intensify therapy in a timely fashion |
| • Provide acute hospital care with access to all medications |
| • Evaluate RV function and stability over long term |
| • Improve connection to PHA and other support resources |
| • Offer participation by patients and families in PAH support groups |
| • Enhance awareness of and access to clinical trials |
| • Optimize access to and timing of lung transplantation |

Table 1. Partial advantages of referral to and collaboration with an expert specialty center for PAH

Abbreviations: PHA=Pulmonary Hypertension Association; RV=right ventricle

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opportunities for care obtained at accredited specialty centers to optimize PAH outcomes. Table 1 summarizes many of these anticipated benefits of referral to and collaboration with specialized treatment centers for PAH.

In summary, there is substantial evidence that referral for PAH care to specialty centers will improve outcomes. With the upcoming implementation of PHA accreditation of PHCC, patients and providers will soon have assurance that the designated specialty centers have the expertise they are seeking and deserve. This program will, I believe, reinforce the benefits of the medical specialty movement that began more than 150 years ago.

References
**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.
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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 patients1,2 and 44 meters (144 feet) for those on ADCIRCA monotherapy1,2.

Clinically proven to reduce risk of clinical worsening vs placebo at 16 weeks3,4

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**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 therapy.1,2

*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 class.1

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

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**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

Cardiovascular Effects: Discus with patients the appropriate action to take in the event that they experience anginal chest pain or other symptoms following intake of ADICIRCA. At least 48 hours should elapse after the last dose of ADICIRCA before taking nitrates. If a patient has taken ADICIRCA within 48 hours, administer nitrates under close medical supervision with appropriate hemodynamic monitoring. Patients who experience angina after pain associated with taking ADICIRCA 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 ADICIRCA, 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. Intracoronary injection of ADICIRCA on the nitric oxide/GMP pathway, presence of any organic nitrates, or relevant clinical settings with pulmonary veno-occlusive disease (PVOD). Since there are no clinical data on administration of ADICIRCA to patients with veno-occlusive disease, administration of ADICIRCA to such patients is not recommended. Should signs of pulmonary edema occur when ADICIRCA is administered, the possibility of associated PVOD should be considered. There is a lack of data on safety and efficacy in the following groups who were specifically excluded from the PAH clinical trials:

- Patients with clinically significant aortic and mitral valve disease
- Patients with pericardial constriction
- Patients with restrictive or congestive cardiomyopathy
- Patients with significant left ventricular dysfunction
- Patients with life-threatening arrhythmias
- Patients with symptomatic coronary artery disease
- Patients with hypertension (>150/90 mm Hg) or uncontrolled hypertension

Use with Alpha-Blockers and Antihypertensives — PDE5 inhibitors, including ADICIRCA, and alpha-adrenergic blocking agents are vasodilators with blood pressure-lowering effects. When vasodilators are used in combination, an additive effect on blood pressure may be anticipated. In some patients with concomitant use of these two drug classes patients may have lower blood pressure significantly, which may lead to symptomatic hypotension (e.g., fainting). Safety of combined use of PDE5 inhibitors and ADICIRCA has not been established in patients with impaired hepatic function (Child–Pugh Class B). Use of ADICIRCA in these patients has not been studied. Inform patients taking ADICIRCA 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 medical emergency medical attention. ADICIRCA should be used with caution in patients with conditions that might predispose them to priapism (such as sickle cell anemia, multiple myeloma, or leukaemia), or in patients with anatomical deformations of the penis (such as angulated penis, Peyronie’s disease). Effects on Bleeding: ADICIRCA is found in platelets. When administered in combination with aspirin, tadalafil 20 mg did not prolong bleeding time, relative to aspirin alone. ADICIRCA has not been administered to patients with bleeding disorders or significant active peptic ulceration. Although ADICIRCA 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
- Pruritus

**CLINICAL TRIALS EXPERIENCE**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Tadalafil was administered to 936 patients with PAH during clinical trials worldwide. In trials of ADICIRCA, a total of 311 and 251 subjects have been treated for at least 182 days and 360 days, respectively. The overall rates of discontinuation because of an adverse event (AE) in the placebo-controlled trial were 4% for ADICIRCA 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 ADICIRCA 40 mg was 4% compared to 5% in placebo-treated patients. In the placebo-controlled study, the aortic and mitral AEs were generally transient and mild and to moderate in intensity. Table 1 presents treatment-emergent adverse events reported by ≥2% of patients in the ADICIRCA 40 mg group and occurring more frequently than placebo.

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (%)</th>
<th>ADICIRCA 40 mg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Back Pain</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Nasal Congestion (Including sinus congestion)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Postmarketing Experience: The following adverse reactions have been identified from 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 reliably estimate a causal relationship to drug exposure. The list does not include adverse events that are reported from clinical trials and that are listed elsewhere in this section.

**Cardiovascular and Cerebrovascular** — Serious cardiovascular events, including myocardial infarction, sudden death, stroke, chest pain, palpitations, and tachycardia, have been reported in temporal association with the use of tadalafil. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of tadalafil without sexual activity. Others were reported to have occurred hours to days after the use of tadalafil and sexual activity. It is not possible to determine whether these events are related directly to tadalafil, to sexual activity, to the patient’s underlying cardiovascular disease, to a combination of these factors, or to other factors.

**Body as a whole** — Hypersensitivity reactions including urticaria, Stevens–Johnson syndrome, and exfoliative dermatitis. Nausea — Migraine, seizure and seizure recurrence, and transient global amnesia.

**Ophthalmologic** — Visual field defect, retinal vein occlusion, and retinal artery occlusion. Non–arteritic anterior ischemic optic neuropathy (NAION), a cause of sudden loss of vision, has been reported rarely in patients using other PDE5 inhibitors. In clinical trials, incidence of NAION in patients taking ADICIRCA was 4% compared to 5% in placebo-treated patients. The rates of discontinuation because of AEs, other than those related to worsening of PAH, in patients treated with ADICIRCA 40 mg was 4% compared to 5% in placebo-treated patients. It is not possible to determine whether these events are related directly to the use of PDE5 inhibitors, to the patient’s underlying vascular risk factors or anatomic defects, to a
combination of these factors, or to other factors.

**Adverse Reactions:**

- **Cardiac:** Cardiac arrest, myocardial infarction, angina, unstable angina. Cardiac ischemia, palpitations, heart failure, and transient ischemic attack.
- **CNS:** Headache, dizziness, syncope, insomnia, anxiety, depression, paresthesia, ringing in the ears.
- **Respiratory:** Upper respiratory tract infection, bronchitis, sinusitis, dyspnea.
- **Gastrointestinal:** Constipation, diarrhea, nausea.
- **Musculoskeletal:** Muscle cramps, myalgia.
- **Skin:** Rash, urticaria, angioedema.
- **Hematologic:** Anemia, leukopenia, thrombocytopenia.
- **Special Senses:** Otologic adverse events, including sudden decrease or loss of hearing.

**Drug Interactions:**

- **Hepatic:** Tadalafil is metabolized by CYP3A4 and CYP2C8. It is a substrate of CYP3A4, CYP2C8, and P-gp (P-glycoprotein).
- **Renal:** Tadalafil is not removed by hemodialysis.
- **CYP3A4 Inhibitors:** Tadalafil is metabolized by CYP3A4. Use of CYP3A4 inhibitors with tadalafil can increase tadalafil plasma concentrations.
- **CYP3A4 Inducers:** Tadalafil is not affected by CYP3A4 inducers.

**Pregnancy and Lactation:**

- **Pregnancy:** Tadalafil is not a known teratogen. Use during pregnancy should be avoided.
- **Lactation:** Tadalafil is excreted into human milk. It is not known whether tadalafil is excreted in human milk at concentrations that could affect nursing infants. Breastfeeding is not recommended while taking tadalafil.

**Clinical Pharmacology:**

- **Pharmacokinetics:** Tadalafil is rapidly absorbed after oral administration. Peak plasma concentrations are achieved within 1.5 hours. The drug is extensively metabolized in the liver and excreted in the urine and feces. It has a long half-life of around 17 hours.
- **Drug-Drug Interactions:** Tadalafil inhibits CYP3A4 and CYP2C8. It can increase the plasma concentrations of drugs that are metabolized by these enzymes. Conversely, it can be affected by drugs that induce CYP3A4 or CYP2C8.

**Overdosage:**

- **Symptoms:** Headache, nausea, flushing, dizziness, and hypotension.
- **Treatment:** Supportive care, including monitoring of vital signs andGeneral Medical Support. Use of specific antidotes is not recommended.
What Should FDA Know about PAH?
Encourage your patients to join a rare conversation with FDA drug reviewers about living with PAH and the impact of current treatments on daily life.
Tuesday May 13, 2014
1:00-5:00 p.m. EST
10903 New Hampshire Avenue
Silver Spring, MD 20993 (FDA Campus)

In-person attendance is encouraged, but webcast participation is available. PHA will provide buses from our New York and Maryland offices. All members of the PHA community are welcome to attend, but FDA will focus on speaking with persons currently living with PAH. Learn more and register at www.PHAssociation.org/FDARegistration

Help Your Patients Find the Resources They Need
Help your patients take control of their PH diagnosis with PHA’s free resources for patients and caregivers. These materials help patients and their families understand PH and connect with support resources. Free resources include:

- Envelope of Hope: This free kit for newly diagnosed PH patients provides information about PH, finding specialists, organizing treatment plans, and connecting with other patients. Patients can request information kits directly at: www.PHAssociation.org/EnvelopeofHope.

- Empowered Patient Online Toolkit: This toolkit helps patients create their own PH-specific medical binder with their medical appointments, medical histories, medication dosages, pharmacy numbers, insurance plans, and more. Patients can download this medical binder to bring to all medical appointments at: www.PHAssociation.org/OnlineToolkit.

- Coping with PH Guides: This series of downloadable coping guides for newly diagnosed patients, long-term survivors, parents, caregivers, and teens address the emotional, social, and spiritual components of living with PH. www.PHAssociation.org/Coping

PHA’s History of PH Series
The recordings of PHA’s History of Pulmonary Hypertension two-part webinar series are now available online. Presenters include:

- David Badesch, MD, University of Colorado, Denver
- Bruce Brundage, MD, St. Charles Medical Center - Bend
- C. Gregory Elliott, MD, Intermountain Medical Center
- Michael McGoon, MD, Mayo Clinic
- Stephen Mathai, MD, MHS, Johns Hopkins University School of Medicine
- Stuart Rich, MD, University of Chicago
- Lewis Rubin, MD, University of California, San Diego, Thornton Hospital

You can view the webinars at www.phassociation.org/HistoryOfPHMechanismsAndPhysiology and www.phassociation.org/HistoryOfPHProgressInClinicalManagement.
INDICATIONS

- Adempas (riociguat) tablets 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.
- 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.

For more information visit Adempas-US.com.

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.

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 nitrate) in any form.
- Concomitant administration with phosphodiesterase (PDE) inhibitors, including specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline).

Warnings and Precautions

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.

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.
- 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 program, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0.0% of placebo patients. Serious hemoptysis occurred in 5 (1.0%) 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.

Most Common Adverse Reactions

The most common adverse reactions occurring more frequently (≥ 3%) on Adempas than placebo were headache (27% vs 18%), dyspepsia/gastritis (21% vs 8%), dizziness (20% vs 13%), nausea (14% vs 11%), diarrhea (12% vs 8%), hypertension (10% vs 4%), vomiting (10% vs 7%), anemia (7% vs 2%), gastroesophageal reflux disease (5% vs 2%), and constipation (5% vs 1%).

Other events that were seen more frequently in Adempas compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distension and peripheral edema.

For additional important risk and use information, please see brief summary of full Prescribing Information on adjacent page.
Adempas (riociguat) tablets, for oral use

Initial U.S. Approval: 2013

BRIEF SUMMARY of prescribing information

CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Do not administer Adempas to a pregnant female because it may cause fetal harm (see Contraindications (4.1), Use in Specific Populations (8.1)).

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 (8.1)).

For all female patients, Adempas is available only through a restricted program called the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program (see Warnings and Precautions (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 efficacy included predominantly patients with WHO functional classes 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 teratogenic in animals. Adempas was studied in women of reproductive potential, but the disease state itself is associated with adverse outcomes such as fetal loss. Therefore, 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 (2.9), Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.6)).

4.2 Nitrates and Nitric Oxide Donors

Co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) is contraindicated (see Drug Interactions (7.1), Clinical Pharmacology (12.2)).

4.3 Phosphodiesterase Inhibitors

Concomitant administration of Adempas with phosphodiesterase (PDE) inhibitors, including 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), 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 (2.9), 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 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)).

• Prescribers must be certified with the program and must only dispense to females who are enrolled in the program.

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 diuretics or strong CYP and P-gp/BCRP inhibitors (see Drug Interactions (7.2), Clinical Pharmacology (12.3)).

5.4 Bleeding

In the placebo-controlled clinical trials program, serious bleeding occurred in 2.4% of patients taking Adempas compared to 0.0% 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.

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 events in Table 1 can be ascribed to the vasodilatory mechanism of action of Adempas. The overall rates of discontinuation due to an adverse event in the pivotal placebo-controlled trials were 2.9% for Adempas and 5.1% for placebo (pooled data).

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Adempas % (n=490)</th>
<th>Placebo % (n=214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Dyspepsa 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 riociguat compared to placebo and potentially related to treatment were: palpitations, nasal congestion, epistaxis, dysphagia, abdominal distention 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 (4.1), Clinical Pharmacology (12.2)).

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

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 Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].

Strong CYP and P-gp/BCRP inhibitors: Concomitant use of riociguat with strong cytochrome CYP inhibitors and P-gp/BCRP inhibitors such as azole antifungalics (for example, ketoconazole, itraconazole) or HIV 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 on treatment with strong CYP and P-gp/BCRP inhibitors. A dose reduction should be considered in patients who may not tolerate the hypotensive effect of riociguat [see Dosage and Administration (2.5), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Risk Summary

Adempas may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. Adempas was teratogenic and embryotoxic in rats at doses with exposures approximately 3 times the human exposure. In rabbits, riociguat led to abortions at 5 times the human fetal toxicity at doses with exposures approximately 15 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 Contraindications (4.1)].

Animal Data

In rats administered riociguat orally (1, 5, 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 is approximately 0.15 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). Plasma exposure at the highest dose is approximately 3 times that in humans at the MRHD while exposure at the mid-dose is approximately 0.5 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 starting at the mid-dose of 1.5 mg/kg, and an increase in resorptions was observed at 5 mg/kg/day. Plasma exposures at these doses were 5 times and 15 times the human dose at MRHD respectively.

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.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Adempas, 23% were 65 and over, and 6% were 75 and over [see Clinical Studies (14)]. No overall differences in safety or effectiveness were observed between these subjects 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, one month before starting treatment, and one month after discontinuation of treatment with Adempas. Advise patients to contact their health care provider if they become pregnant or suspect they may be pregnant. Counsel patients on the risk to the fetus [see Boxed Warning and Dosage and Administration (2.2)].

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 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].

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 her 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 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 Pharmaceuticals Inc.
Whippany, NJ 07981

Manufactured in Germany

Issued October 2013

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Program Announcement:

New Application Deadline: June 12, 2014  
New Application Deadline: October 12, 2014  
Resubmission Deadline: July 12, 2014
Resubmission Deadline: November 12, 2014

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

Jointly Sponsored

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

**PURPOSE: K08**
- To support the development of outstanding clinician research scientists in the area of pulmonary hypertension.
- To provide specialized study for clinically trained professionals who are committed to a career in research in pulmonary hypertension and have the potential to develop into independent investigators.
- To support a 3 to 5 year period of supervised research experience that integrates didactic studies with laboratory or clinically based research.
- To support research that has both intrinsic research importance and merit as a vehicle for learning the methodology, theories, and conceptualizations necessary for a well-trained independent researcher.

**MECHANISM:**

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

**FUNDING:**

The award will be funded by PHA and NHLBI and the K08 and/or the K23 will be awarded in 2013.

**PURPOSE: K23**
- To support career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research.
- To support a 3 to 5 year period of supervised study and research for clinically trained professionals who have the potential to develop into productive, clinical investigators focusing on patient-oriented research in pulmonary hypertension.
- To support patient-oriented research, which is defined as research conducted with human subjects (or on material of human origin, such as tissues, specimens, and cognitive phenomena) for which an investigator directly interacts with human subjects.
- To support areas of research that include: 1) mechanisms of human disease; 2) therapeutic interventions; 3) clinical trials; and 4) development of new technologies.

Learn about all of PHA’s research opportunities at www.PHAssociation.org/MedicalProfessionals/PHAResearchProgram

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

New Application Deadline: June 12, 2014  
Resubmission Deadline: July 12, 2014

New Application Deadline: October 12, 2014  
Resubmission Deadline: November 12, 2014

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

Jointly Sponsored

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

PURPOSE: K08
• To support the development of outstanding clinician research scientists in the area of pulmonary hypertension.
• To provide specialized study for clinically trained professionals who are committed to a career in research in pulmonary hypertension and have the potential to develop into independent investigators.
• To support a 3 to 5 year period of supervised research experience that integrates didactic studies with laboratory or clinically based research.
• To support research that has both intrinsic research importance and merit as a vehicle for learning the methodology, theories, and conceptualizations necessary for a well-trained independent researcher.

PURPOSE: K23
• To support career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research.
• To support a 3 to 5 year period of supervised study and research for clinically trained professionals who have the potential to develop into productive, clinical investigators focusing on patient-oriented research in pulmonary hypertension.
• To support patient-oriented research, which is defined as research conducted with human subjects (or on material of human origin, such as tissues, specimens, and cognitive phenomena) for which an investigator directly interacts with human subjects.
• To support areas of research that include: 1) mechanisms of human disease; 2) therapeutic interventions; 3) clinical trials; and 4) development of new technologies.

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.

Learn about all of PHA’s research opportunities at www.PHAssociation.org/MedicalProfessionals/PHAResearchProgram

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