CHEST™

# Pharmacologic Therapy for Pulmonary Arterial Hypertension in Adults

## CHEST Guideline and Expert Panel Report

*Darren B. Taichman, MD, PhD, FCCP; Joe Ornelas, MS; Lorinda Chung, MD; James R. Klinger, MD, FCCP; Sandra Lewis, PhD; Jess Mandel, MD; Harold I. Palevsky, MD, FCCP; Stuart Rich, MD, FCCP; Namita Sood, MD, FCCP; Erika B. Rosenzweig, MD; Terence K. Trow, MD, FCCP; Rex Yung, MD, FCCP; C. Gregory Elliott, MD, FCCP; and David B. Badesch, MD, FCCP*

**OBJECTIVE:** Choices of pharmacologic therapies for pulmonary arterial hypertension (PAH) are ideally guided by high-level evidence. The objective of this guideline is to provide clinicians advice regarding pharmacologic therapy for adult patients with PAH as informed by available evidence.

**METHODS:** This guideline was based on systematic reviews of English language evidence published between 1990 and November 2013, identified using the MEDLINE and Cochrane Library databases. The strength of available evidence was graded using the Grades of Recommendations, Assessment, Development, and Evaluation methodology. Guideline recommendations, or consensus statements when available evidence was insufficient to support recommendations, were developed using a modified Delphi technique to achieve consensus.

**RESULTS:** Available evidence is limited in its ability to support high-level recommendations. Therefore, we drafted consensus statements to address many clinical questions regarding pharmacotherapy for patients with PAH. A total of 79 recommendations or consensus statements were adopted and graded.

**CONCLUSIONS:** Clinical decisions regarding pharmacotherapy for PAH should be guided by high-level recommendations when sufficient evidence is available. Absent higher level evidence, consensus statements based upon available information must be used. Further studies are needed to address the gaps in available knowledge regarding optimal pharmacotherapy for PAH.

CHEST 2014; 146(2):449-475

**ABBREVIATIONS:** 6MWD = 6-min walk distance; AHRQ = Agency for Healthcare Research and Quality; ARIES = Ambrisentan in Pulmonary Arterial Hypertension, Randomized Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study; BNP = brain natriuretic peptide; CB = consensus-based; CCB = calcium channel blocker; CO = cardiac output; COI = conflict of interest; CTEPH = chronic thromboembolic pulmonary hypertension; EPC = Evidence-Based Practice Center; ETRA = endothelin receptor antagonist; FC = functional class; FDA = US Food and Drug Administration; GOC = Guidelines Oversight Committee; GRADE = Grades of Recommendations, Assessment, Development, and Evaluation; HR = hazard ratio; IOM = Institute of Medicine; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase-5; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; WHO = World Health Organization

Manuscript received April 1, 2014; revision accepted May 5, 2014; originally published Online First June 17, 2014.

**AFFILIATIONS:** From the University of Pennsylvania (Drs Taichman and Palevsky), Philadelphia, PA; CHEST (Mr Ornelas and Dr Lewis), Glenview, IL; Stanford University and Palo Alto VA Health Care System (Dr Chung), Palo Alto, CA; Brown University (Dr Klinger), Providence, RI; the University of California (Dr Mandel), San Diego, CA; the University of Chicago (Dr Rich), Chicago, IL; Ohio State University (Dr Sood), Columbus, OH; Columbia University Medical Center (Dr Rosenzweig), New York, NY; Yale University (Dr Trow), New Haven, CT; Johns Hopkins University

## Summary of Recommendations

### Pharmacologic Therapy for Pulmonary Arterial Hypertension in Adults

**1. We suggest that the severity of a pulmonary arterial hypertension (PAH) patient's disease be evaluated in a systematic and consistent manner, using a combination of World Health Organization (WHO) functional class (FC), exercise capacity, echocardiographic, laboratory and hemodynamic variables in order to inform therapeutic decisions** (Grade CB).

**2. We suggest that, whenever possible, all PAH patients be evaluated promptly at a center with expertise in the diagnosis of PAH, ideally prior to the initiation of therapy** (Grade CB).

**3. We suggest collaborative and closely coordinated care of PAH patients involving the expertise of both local physicians and those with expertise in PAH care** (Grade CB).

*Remark:* Appropriate care may require the coordinated efforts of cardiologists, pulmonologists, rheumatologists, primary care, or other specialties.

#### *Treatment Naive PAH Patients Without Symptoms (WHO FC I) and Patients at Increased Risk for the Development of PAH*

**4. For treatment naive PAH patients with WHO FC I symptoms, we suggest continued monitoring for the development of symptoms that would signal disease progression and warrant the initiation of pharmacotherapy** (Grade CB).

**5. We suggest that patients at risk for the development of PAH (eg, patients with systemic sclerosis or the presence of a known mutation placing the patient at risk for PAH) be monitored for the development of symptoms of PAH** (Grade CB).

**6. We suggest also that contributing causes of PH (eg, sleep apnea and systemic hypertension) in patients with PAH be treated aggressively** (Grade CB).

### Symptomatic Patients With PAH

#### *Vasoreactivity Testing and Use of Calcium Channel Blockers*

**7. We suggest that patients with PAH, in the absence of contraindications, should undergo acute**

FOR EDITORIAL COMMENT SEE PAGE 239
SEE RELATED ARTICLE PAGE 476

**vasoreactivity testing using a short-acting agent at a center with experience in the performance and interpretation of vasoreactivity testing** (Grade CB).

*Remark:* Contraindications to acute vasoreactivity testing include a low systemic blood pressure, low cardiac output or the presence of FC IV symptoms. Acute vasoreactivity testing may be complicated by hypotension, and the misinterpretation of results may result in the inappropriate exposure of patients to the risks of a treatment trial with calcium channel blockers (CCBs) without the possibility of clinical benefit. Vasoreactivity testing should be performed by individuals with appropriate training in test performance and interpretation.

**8. We suggest that patients with PAH who, in the absence of right-heart failure or contraindications to CCB therapy, demonstrate acute vasoreactivity according to consensus definition, should be considered candidates for a trial of therapy with an oral CCB blocker** (Grade CB).

**9. We suggest that CCBs should not be used empirically to treat PAH in the absence of demonstrated acute vasoreactivity** (Grade CB).

### PAH-Specific Pharmacotherapies

**Patients With WHO FC II Symptoms:**

**For treatment naive PAH patients with WHO FC II symptoms who are not candidates for, or who have failed CCB therapy, we advise monotherapy be initiated with a currently approved endothelin receptor antagonist (ETRA), phosphodiesterase-5 (PDE5) inhibitor, or the soluble guanylate cyclase stimulator riociguat. More specifically in these patients:**

(Dr Yung), Baltimore, MD; the Intermountain Medical Center and the University of Utah (Dr Elliott), Murray, UT; and the University of Colorado (Dr Badesch), Denver, CO.

Drs Elliott and Badesch contributed equally to this manuscript.

**FUNDING/SUPPORT:** This study was funded in total by internal funds from the American College of Chest Physicians.



**CORRESPONDENCE TO:** Joe Ornelas, MS, CHEST, 2595 Patriot Blvd, Glenview, IL 60026; e-mail: jornelas@chestnet.org



**DOI:** 10.1378/chest.14-0793

**10. We recommend ambrisentan to improve 6-min walk distance (6MWD)** (Grade 1C)**.**

**11-12. We suggest bosentan to delay time to clinical worsening** (Grade CB) **and improve cardiopulmonary hemodynamics.**

**13. We suggest macitentan to delay the time to clinical worsening** (Grade CB)**.**

**14. We recommend sildenafil to improve 6MWD** (Grade 1C)**.**

**15. We suggest tadalafil to improve 6MWD** (Grade CB)**.**

**16-19. We suggest riociguat to improve 6MWD** (Grade CB)**, improve WHO FC** (Grade CB)**, delay the time to clinical worsening** (Grade CB) **and improve cardiopulmonary hemodynamics.**

**20. We suggest also that parenteral or inhaled prostanoids not be chosen as initial therapy for treatment naive PAH patients with WHO FC II symptoms or as second line agents for PAH patients with WHO FC II symptoms who have not met their treatment goals** (Grade CB)**.**

**Patients With WHO FC III Symptoms:**

**For treatment-naive PAH patients with WHO FC III symptoms who are not candidates for, or who have failed CCB therapy, we advise monotherapy be initiated with a currently approved ETRA, a PDE5 inhibitor, or the soluble guanylate cyclase stimulator riociguat. More specifically in these patients:**

**21. We recommend the use of bosentan to improve 6MWD** (Grade 1B)**.**

**22-23. We suggest the use of bosentan to decrease hospitalizations related to PAH in the short-term** (Grade 2C)**, and to improve cardiopulmonary hemodynamics.**

**24. We recommend the use of ambrisentan to improve 6MWD** (Grade 1C)**.**

**25-26. We suggest macitentan to improve WHO FC** (Grade CB) **and delay the time to clinical worsening** (Grade CB)**.**

**27-29. We recommend the use of sildenafil to improve 6MWD** (Grade 1C) **and to improve WHO FC** (Grade CB)**. We suggest the use of sildenafil to improve cardiopulmonary hemodynamics.**

**30-33. We suggest the use of tadalafil to improve 6MWD** (Grade CB)**, to improve WHO FC** (Grade CB)**, to delay time to clinical worsening** (Grade CB) **and to improve cardiopulmonary hemodynamics.**

**34-37. We suggest riociguat to improve 6MWD** (Grade CB)**, improve WHO FC** (Grade CB)**, delay the time to clinical worsening** (Grade CB) **and improve cardiopulmonary hemodynamics.**

**For treatment naive PAH patients with WHO FC III symptoms who have evidence of rapid progression of their disease, or other markers of a poor clinical prognosis, we advise consideration of initial treatment with a parenteral prostanoid. More specifically in these patients:**

**38-40. We suggest continuous IV epoprostenol to improve FC** (Grade CB)**, improve 6MWD** (Grade CB)**, and improve cardiopulmonary hemodynamics.**

**41. We suggest continuous IV treprostinil to improve 6MWD** (Grade CB)**.**

**42-43. We suggest continuous subcutaneous treprostinil to improve 6MWD** (Grade CB) **and improve cardiopulmonary hemodynamics.**

**For PAH patients in WHO FC III who have evidence of progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents, we advise consideration of the addition of a parenteral or inhaled prostanoid. More specifically in these patients:**

**44-46. We suggest IV epoprostenol to improve WHO FC** (Grade CB)**, improve 6MWD** (Grade CB)**, and improve cardiopulmonary hemodynamics.**

**47-48. We suggest IV treprostinil to improve 6MWD** (Grade CB) **and improve cardiopulmonary hemodynamics.**

**49. In patients with PAH who remain symptomatic on stable and appropriate doses of an endothelin receptor antagonist (ETRA) or a PDE5 inhibitor, we suggest the addition of inhaled treprostinil to improve 6MWD** (Grade 2C)**.**

*Remark:* The usual initial dose of inhaled treprostinil is 3 inhalations (18 μg) every 6 h. However, optimal effect of inhaled treprostinil may require titrating treprostinil doses up to 9 inhalations (54 μg) every 6 h.

**50-51. In patients with PAH who remain symptomatic on stable and appropriate doses of an ETRA or a PDE5 inhibitor, we suggest the addition of inhaled iloprost to improve WHO FC** (Grade CB) **and delay the time to clinical worsening** (Grade CB)**.**

**Patients With WHO FC IV Symptoms:**

**For treatment naive PAH patients in WHO FC IV, we advise initiation of monotherapy with a parenteral prostanoid agent. More specifically in these patients:**

**52-54. We suggest continuous IV epoprostenol to improve WHO FC** (Grade CB)**, improve 6MWD** (Grade CB)**, and improve cardiopulmonary hemodynamics.**

**55. We suggest continuous IV treprostinil to improve 6MWD** (Grade CB)**.**

**56-57. We suggest continuous subcutaneous treprostinil to improve 6MWD** (Grade CB) **and improve cardiopulmonary hemodynamics.**

**For treatment naive PAH patients in WHO FC IV who are unable or do not desire to manage parenteral prostanoid therapy, we advise treatment with an inhaled prostanoid in combination with an ETRA. More specifically in these patients:**

**58-59. We suggest bosentan to improve 6MWD** (Grade 2B) **and cardiopulmonary hemodynamics.**

**60-61. We suggest inhaled iloprost to improve 6MWD** (Grade CB)**, and improve WHO FC** (Grade CB)**.**

**62. We suggest inhaled treprostinil (in combination only) to improve 6MWD** (Grade CB)**.**

**PAH Patients on Established PAH-Specific Therapy:**

**63. In PAH patients initiating therapy with IV epoprostenol, we suggest against the routine simultaneous initiation of bosentan** (Grade CB)**.**

**For WHO FC III or IV PAH patients with unacceptable clinical status despite established PAH-specific monotherapy, we advise addition of a second class of PAH therapy to improve exercise capacity. Such patients are ideally evaluated at centers with expertise in the evaluation and treatment of complex patients with PAH. More specifically:**

**64. In patients with PAH who remain symptomatic on stable doses of an ETRA or a PDE5 inhibitor, we suggest the addition of inhaled iloprost to improve 6MWD** (Grade CB)**.**

**65. In patients with PAH who remain symptomatic on stable doses of an ETRA or a PDE5 inhibitor, we recommend the addition of inhaled treprostinil to improve 6MWD** (Grade 1C)**.**

*Remark:* The usual initial dose of inhaled treprostinil is 3 inhalations (18 μg) every 6 h. However, optimal effect of inhaled treprostinil may require titrating treprostinil doses up to 9 inhalations (54 μg) every 6 h.

**66. In PAH patients who remain symptomatic on stable doses of established IV epoprostenol, we suggest the addition of sildenafil or up titration of epoprostenol to improve 6MWD** (Grade CB)**.**

**67-70. In patients with PAH who remain symptomatic on stable doses of bosentan, ambrisentan or an inhaled prostanoid, we suggest the addition of the soluble guanylate cyclase stimulator riociguat to improve 6MWD** (Grade CB)**, WHO FC** (Grade CB) **and cardiopulmonary hemodynamics and to delay the time to clinical worsening** (Grade CB)**.**

**71-73. In patients with PAH who remain symptomatic on stable doses of a PDE5 inhibitor or an inhaled prostanoid we suggest macitentan to improve 6MWD** (Grade CB)**, WHO FC** (Grade CB) **and to delay the time to clinical worsening** (Grade CB)**.**

**74. For WHO FC III or IV PAH patients with unacceptable or deteriorating clinical status despite established PAH-specific therapy with two classes of PAH pharmacotherapy, we suggest addition of a third class of PAH therapy** (Grade CB)**.**

*Remark:* Such patients are ideally evaluated at centers with expertise in the evaluation and treatment of complex patients with PAH.

## Specific Patient Situations

### *Pregnancy*

**75. In patients with PAH, we suggest that pregnancy be avoided** (Grade CB)**.**

*Remark:* Estrogen-containing contraceptives may increase the risk of VTE and are not recommended for women with childbearing potential who have PAH. Additionally, the ETRA bosentan may decrease the efficacy of hormonal contraception. Bosentan, ambrisentan, macitentan and riociguat are contraindicated in pregnancy (category X; evidence of serious fetal abnormalities) and dual mechanical barrier contraceptive techniques are recommended in female patients of childbearing age taking these medications.

**76. When pregnancy does occur, we suggest care at a pulmonary hypertension center, using a multidisciplinary approach including the pulmonary hypertension, the high-risk obstetrical and cardiovascular anesthesiology services** (Grade CB)**.**

### *Altitude and Air Travel*

**77. In patients with PAH, we suggest that exposure to high altitude be avoided, and that supplemental oxygen be used as needed during altitude exposure or air travel to maintain oxygen saturations greater than 91%** (Grade CB)**.**

*Remark:* Patients with borderline oxygen saturations at sea level may require 3-4 L per minute of supplemental oxygen under these conditions, and those already using supplemental oxygen at sea level should increase their oxygen flow rate on commercial aircraft.

### *Vaccinations*

**78. In patients with PAH, we suggest maintaining current immunization against influenza and pneumococcal pneumonia** (Grade CB)**.**

### *Surgery*

**79. In patients with PAH, we suggest avoiding nonessential surgery, and when surgery is necessary we suggest care at a pulmonary hypertension center, using a multidisciplinary approach including the pulmonary hypertension team, the surgical service, and cardiovascular anesthesiology with careful monitoring and management of clinical status, oxygenation and hemodynamics postoperatively** (Grade CB)**.**

## Introduction

Pulmonary arterial hypertension (PAH) remains a highly morbid disease with high mortality. Despite a recent growth in therapeutic options, clinicians and their patients continue to struggle with questions regarding pharmacologic treatments. This document aims to provide practical guidance to clinicians faced with common questions regarding the use of available pharmacotherapies for the treatment of patients with PAH. We sought to apply a rigorous process to the collection and assessment of evidence and to make guideline recommendations informed and supported by that evidence. Unfortunately, rigorous data needed to address important questions faced by clinicians when treating patients with PAH are often absent or insufficient. We therefore present a hybrid document. When sufficiently strong evidence from randomized clinical trials addressing a clinically important question is available, we have based our guideline recommendation statements upon them. When evidence is absent or insufficient to provide evidence-based guideline recommendation statements, we provide our best expert advice as consensus statements with the goal of helping clinicians navigate important therapeutic questions.

We emphasize that accurate and timely diagnosis must precede therapy for PAH. Pulmonary hypertension (PH) is categorized according to five groups. In addition to PAH (group 1), PH may be due to left-sided heart disease (group 2), lung diseases and/or hypoxia (group 3), chronic thromboembolic pulmonary hypertension (CTEPH, group 4), or unclear multifactorial mechanisms (group 5).[1] It is a critical responsibility of the clinician to ensure that an accurate diagnosis is established, and readers are referred to previously published guidelines by the American College of Chest Physicians (CHEST) and other organizations on the evaluation of PH and diagnosis of PAH.[2-4] The recommendations in this guideline are for the treatment of patients with PAH and should not be applied to the treatment of patients with other types of PH. None of the drugs currently approved for therapy for PAH are approved for therapy for patients with PH due to left-sided heart disease or chronic hypoxemic lung disease. The limited evidence available regarding the use of these drugs in patients with PH due to left-sided heart disease or hypoxemic lung disease has not demonstrated benefit overall and in some cases suggests the potential for significant harm. Further, failure to correctly identify or address the cause of PH may deny the patient beneficial treatment (eg, for left-sided heart disease). Although one drug approved for treatment of PAH has been shown to be beneficial in patients with CTEPH not amenable to surgical thromboendarterectomy, surgery remains the optimal therapy for many patients with CTEPH, and patients should be evaluated promptly for consideration of thromboendarterectomy at a center sufficiently experienced with this procedure.[5]

Standards for the development of clinical guidelines have evolved, and the approach to the grading of evidence has become more rigorous since the last CHEST guideline on PAH.[2,6] As a result, readers may note lower grades assigned to recommendations in this guideline update as compared with the grading of statements recommending similar actions in prior CHEST guidelines on PAH or related recommendations of other organizations. This may seem paradoxical at first, as the evidence upon which the recommendations are based remains, in many cases, largely the same. The change in grading reflects the more rigorous standard now being applied by CHEST to the evaluation of evidence. Further, some equivalent and parallel trials of individual drugs have been conducted and reported independently, whereas others were reported as single larger investigations. We recognize that this may influence assessments of the overall strengths of evidence available, but we judged it best to adhere to a consistent approach based upon how studies were accepted by the US Food and Drug Administration (FDA) and reported.

Although patients meeting diagnostic criteria for PAH share many clinical characteristics, we emphasize that a wide variety of underlying diseases and risk factors may lead to PAH, likely with differing etiologic mechanisms. Similarly, all patients classified as having idiopathic PAH by the exclusion of known risk factors for PAH may not suffer from the same pathobiologic processes. Clinical trials of PAH-specific therapies have generally enrolled patients under the broad definition of PAH, although with an overall predominance of patients with either idiopathic PAH or PAH associated with systemic sclerosis. It is important to recognize the limitations in knowledge regarding the efficacy of available agents in all forms of PAH. Further, with the exception of calcium channel blockers (CCBs), we lack effective means of predicting which patients with PAH may benefit from individual agents.

This guideline addresses only drugs that were approved by the US FDA for the management of PAH symptoms at the time that the guideline was developed (with the exception of CCBs, which we include because of their continued importance as PAH-specific therapy for a small but important subgroup of patients with PAH). Further, as the US FDA has approved drugs for PAH therapy in part according to a patient's World Health Organization (WHO) functional classification, and because we believe it will best assist clinicians to use this guideline, we have organized our recommendations around such a classification. We recognize the limitations of the WHO functional classification[7] and that other variables must be considered simultaneously (such as exercise capacity, right ventricular function, hemodynamics, economic and other social factors, quality of life, and, most importantly, patient preferences). We recognize also the limitations of the hemodynamic, exercise capacity (6-min walk distance [6MWD]),[8] and clinical worsening end points we present in this guideline for clinicians to consider when choosing pharmacologic therapy. Our knowledge of the relative importance of these end points and how changes in each or groups of end points impact patients' lives is limited.[9]

Although we stress the importance of the involvement of clinicians with expertise in the evaluation and treatment of PH in the management of patients with PAH, the target audience for this guideline is the whole community of clinicians involved in the collaborative care of adult patients with PAH (including cardiologists, nurses, nurse practitioners, primary care internists and family physicians, pulmonologists, and rheumatologists). We do not address therapy for children, and readers are referred to the guidelines of other professional societies.[10]

"Supportive" pharmacologic therapies (eg, diuretics, supplemental oxygen, and so forth) are important in the management of patients with PAH in addition to the "PAH-specific" drugs addressed in this document. We have not performed an updated literature review regarding such supportive care and refer readers to prior CHEST guideline statements regarding this important aspect of PAH care. We remind clinicians of the importance of carefully reviewing prescribing information and consulting reliable resources to check for drug-drug interactions.

No approved therapy for PAH has been shown to prevent progression of the underlying pulmonary vascular disease. PAH remains an incurable disease; currently, clinicians attempt to manage it with pharmacotherapy. Although we believe the outlook for a patient with newly diagnosed PAH has improved, it remains far from adequate or acceptable.

We hope that many of the gaps in the evidence base reflected in this document will be filled before the next update to this guideline. We call upon the community of academic and industry-based researchers in this field to choose carefully those studies that will answer the most important clinical questions so as to best use the limited but generous efforts of our patients, who risk their well-being as volunteer participants in clinical studies.

## Methods

The goal of this CHEST guideline project was to produce clinically relevant and useful recommendations on medical therapies for PAH for clinicians who treat adult patients with PAH. Health-care providers should use these guidelines to assist patients with treatment choices that optimize benefits and minimize harms and burdens.

In 2011, the Institute of Medicine (IOM) released new guideline standards[6] that required significantly more scientific rigor and high-quality evidence to be considered trustworthy. CHEST is committed to upholding the IOM standards in guideline development. However, CHEST realizes clinicians may need to communicate important messages that do not have the necessary associated evidence to be called a "guideline" by the new IOM standards.

In a number of areas related to therapy for PAH, we found the available evidence to be insufficient to support

the more rigorous process necessary to uphold the IOM standards for guidelines. To provide guidance to clinicians in such areas lacking sufficient evidence, the CHEST practice of developing trustworthy consensus statements was used. This hybrid methodology accommodates "very low" or "insufficient" levels of evidence and incorporates both guidelines and consensus statements in the same project. The following document reflects this hybrid approach and follows the standards of the organization to produce credible guidance for physicians and other members of the health-care team.

### *Composition and Selection of Topic Panel Members*

For this CHEST guideline project, a nonconflicted chair was appointed by the organization's Guidelines Oversight Committee (GOC). The chair had the authority to nominate (subject to GOC review and approval) other panelists for specific roles, including participation on the project executive committee and topic editors for the various sections based on drug classes.

All panelists (consisting of the chair, executive committee members, and topic editors) were approved by the CHEST GOC after review of their qualifications and conflict of interest (COI) disclosures. For one of the 12 approved panelists (who had relevant conflicts), a COI management program was followed according to the procedures of the GOC, including abstention from voting on areas related to conflicts (e-Table 1). Throughout the guideline development process all panelists were required to report any new activities that might involve potential COIs for review and approval by the GOC.

### *Identifying and Reviewing the Evidence*

**Key Questions and Systematic Search:** We used the Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Report titled "Pulmonary Arterial Hypertension: Screening, Management, and Treatment,"[11] and chose to focus the development of a guideline document exclusively on one of the three key questions (key question 3) in the report: "For patients with PAH, what are the comparative effectiveness and safety of monotherapy or combination therapy for PAH using calcium channel blockers, prostanoids, endothelin antagonists, or phosphodiesterase inhibitors on intermediate-term and long-term patient outcomes?" As standard practice for the AHRQ, this key question was posted for public comment for 30 days, and later the draft report also was open for public remarks.

For key question 3, the systematic review of the literature was performed by the Duke University Evidence-Based Practice Center (EPC) for AHRQ. Search strategies were developed by the EPC using the National Library of Medicine's medical subject headings keyword nomenclature developed for MEDLINE and adapted for other databases. The EPC searched MEDLINE via PubMed, EMBASE, and the Cochrane Library from 1990 to April 2013, and limited to English language papers and randomized controlled trials (RCTs). Manual searches also supplemented the electronic searches.

Following completion of the EPC-conducted literature review, the endothelin receptor antagonist (ETRA) macitentan and the soluble guanylate cyclase stimulator riociguat were approved by the US FDA for the treatment of PAH, and so the panel completed literature searches to identify RCTs of their use. A key question was formulated in a similar format: "For patients with PAH, what are the comparative effectiveness and safety for PAH using macitentan or riociguat on intermediate-term and long-term patient outcomes?" Search strategies also included medical subject headings keyword nomenclature to search MEDLINE via PubMed and the Cochrane library from 2003 to October 2013, and limited to English language papers and RCTs. Manual searches also supplemented the electronic searches. All gathered references were imported into an electronic database (EndNote ×6; Thomson Reuters) in an electronic folder specific to pharmacotherapy type.

**Study Selection:** PICOTS (Population, Intervention, Comparator, Outcome, Timing, and Setting) criteria (Table 1) were used by the EPC to select articles for inclusion at both the title and abstract and full-text screening stages. Titles and abstracts were examined independently by two reviewers from the EPC for potential relevance. Articles included by the reviewers underwent full-text screening, in which paired researchers from the EPC independently reviewed articles and indicated which ones to include for data extraction. Any disagreements were reconciled through a third party arbitrator at the EPC. All screening decisions were made and tracked in the DistillerSR database (Evidence Partners).

In the literature search performed by the EPC, there were 8,256 citations gathered (3,919 MEDLINE, 36 Cochrane, 4,301 EMBASE). After 1,626 duplicate articles were removed and 46 articles were added manually, a total of 6,676 citations were identified. The screening of abstracts excluded 5,352 articles, and the

**TABLE 1** ] Inclusion Criteria

| Criteria |
|---|
| Population |
| Patients with pulmonary arterial hypertension |
| Intervention |
| Calcium channel blockers (amlodipine, diltiazem, nifedipine) |
| Prostanoids (epoprostenol, treprostinil, iloprost) |
| Endothelin antagonists (bosentan, ambrisentan, macitentan) |
| Phosphodiesterase inhibitors (sildenafil, tadalafil) |
| Soluble guanylate cyclase stimulator (riociguat) |
| Comparators |
| One pharmacotherapy vs another pharmacotherapy |
| Monotherapy vs combination therapy |
| Outcomes |
| Effectiveness of pharmacotherapies |
| Intermediate-term outcomes, such as hemodynamic parameters, dyspnea, and 6-min walk |
| Long-term outcomes, such as functional class, quality of life, right-sided heart failure or right ventricular dysfunction, and mortality |
| Adverse effects of pharmacotherapies |
| Timing |
| Intermediate term (< 120 d) and long term (> 120 d) |
| Setting |
| Inpatient and outpatient |
| Specialty and primary care |
| Study design |
| Randomized controlled trial |
| All sample sizes |
| Publications |
| English-language only |
| Peer-reviewed articles |

Adapted from McCrory et al.[11]

inclusion criteria excluded 1,127 additional articles. The remaining 197 articles representing 186 unique studies passed full-text screening. Of these, 46 articles (37 studies) were relating to monotherapy or combination therapy for PAH using prostanoids, endothelin antagonists, or phosphodiesterase inhibitors. The search for RCTs of the use of CCBs for the therapy for PAH found no studies. As noted above, because CCBs continue to be used and play an important role in the therapy for a small subset of patients with PAH, the guideline panel chose to develop consensus statements on the basis of available nonrandomized studies in this one class of drugs to provide clinically helpful advice for their use.

For the review performed for macitentan and riociguat, there were four citations gathered for macitentan and four citations gathered for riociguat. After the same PICOTS criteria (Table 1) was used by the panel to select articles for inclusion at both the title and abstract and full-text screening stages, one study remained for macitentan and one study remained for riociguat.

### *Summarizing Evidence and Drafting Recommendations*

**Data Extraction and Quality Assessment:** Based on the included studies, the panel constructed data tables that summarized key data elements of each included article. Data elements in the tables included sample size and description, setting description, intervention name and dose, outcome name and values, and associated significance levels.

The critical appraisal quality score of each individual study was determined from the EPC based on the Cochrane Risk of Bias tool.[12] Two raters from the EPC independently evaluated each study, and differences were resolved by consensus. Summary ratings of good, fair, or poor were assigned to each individual study by the EPC based on the tool. For the two articles included from the panel review of macitentan and riociguat, the panel used the same Cochrane Risk of Bias tool to assess study quality. The panel placed the quality scores for each included article as another data element in the constructed data tables.

**Meta-analyses and Pooling of Outcomes:** The data extracted by the panel in the evidence tables from the included studies were pooled according to comparable interventions and outcomes. The panel included only those studies that addressed the use of therapies currently approved by the US FDA.

A meta-analysis using random effects was performed by the panel methodologist to quantitatively synthesize available outcome data by intervention. The relative effects for pooled studies were estimated using an OR for discrete outcomes and mean difference for continuous outcomes. Also, statistical heterogeneity was assessed with an $I^2$ statistic. Meta-analyses were performed and forest plots were constructed using Review Manager, version 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration).

**Evaluating Quality of Bodies of Evidence:** The rating of the quality of the entire body of evidence for each intervention and outcome comparison was assessed by the panel methodologist. Grades of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology was used for summarizing and grading the pooled evidence. Ratings of the pooled evidence started as high quality and were downgraded based on the domains of risk of bias, precision, consistency, directness, and publication bias.[13]

A letter grade (A, B, C or Insufficient) was assigned by the panel to each pooled estimate based on the CHEST grading system[14] (e-Appendix 1) as indicated by the evidence level of the body of literature supporting each intervention and outcome comparison. To be considered at least C-level evidence, two or more studies addressing a particular intervention and outcome were needed.[15] However, pooled estimates were downgraded from higher evidence levels into an "Insufficient" level of evidence if indicated by domains set forth by a GRADE methodologic approach. A meta-analysis was performed only when two or more studies addressed a particular intervention and outcome. All performed meta-analyses are available in e-Figure 1, and profiled evidence is available in e-Table 2. The study data that these pooled estimates were based upon are available in e-Table 3.

**Drafting of Recommendations:** Recommendations were drafted by the panelists assigned to each topic by the project chair, informed from the evidence gathered and aimed to be clinically relevant. Clinically relevant recommendations could not always be directly informed from the data as presented in the studies included in the evidence review. For example, the panel recognized that although changes in individual cardiopulmonary hemodynamic parameters (eg, cardiac output [CO] or pulmonary vascular resistance [PVR]) have been reported in studies included in the evidence review, therapeutic choices would not likely be made on the basis of single hemodynamic parameters. Rather, the panel believed patterns of improvement among multiple cardiopulmonary hemodynamic variables would more likely inform sound clinical recommendations. Because the associated evidence reported outcomes only for specific variables individually (eg, for PVR, mean pulmonary artery pressure [mPAP], CO, cardiac index, right atrial pressure) and not overall patterns of hemodynamic improvement, the panel chose not to grade recommendation statements involving cardiopulmonary hemodynamics but rather simply alert clinicians to when improvements in individual parameters have been found. Similarly, as noted above, despite its limitations, assessments of a patient's WHO FC are frequent starting points in deciding upon therapy and a basis upon which drugs are approved by the FDA. Accordingly, recommendations were organized according to WHO FC. Because available evidence frequently, however, did not report results specifically according to WHO FC, recommendations organized in this manner were downgraded for indirectness according to the GRADE methodology.

Where the evidence level was determined "A," "B," or "C," an evidence-based guideline was pursued. Where the evidence level was determined "Insufficient," a consensus statement was pursued. In these instances, "CB" (consensus-based) was considered the grade. All areas considering CCBs as a therapy were graded as CB because of insufficient evidence. Separately, a number grade (1 or 2) was assigned by the panel to each drafted recommendation based on the CHEST grading system[14] (e-Appendix 1). The number grade is a reflection of the topic editors' consensus on the balance of benefits and harms of treatment, based on their expert

clinical knowledge, experience, and interpretation of the evidence in the gathered literature. Consensus in this instance was determined through open discussion and debate between the two authoring topic editors for each section.

Topic editors drafted initial recommendations, which were combined with the corresponding grade and presented to the entire panel via webinar. Following subsequent group discussions and wording refinements, the entire panel met in Philadelphia in May 2013 to discuss organization and consistency of the recommendations. After the recommendations were in final draft form, they were presented to the entire panel in a formal consensus development process based on the Delphi technique.[16]

**Consensus Development:** The purpose of the Delphi technique in this project was to achieve formal consensus on each recommendation while accounting for group interaction bias and maintaining anonymity among respondents. Using an online survey (www.surveymonkey.com), panelists were requested to vote representing their level of agreement with each presented recommendation based on a five-point scale derived from the GRADE grid.[17] Also, each panelist could provide open-ended feedback on each recommendation with suggested wording edits or general remarks.

Each presented recommendation or consensus-based statement was required to achieve panel consensus (80% of the votes in agreement) to be included in the final manuscript, along with a response rate of ≥ 75% of survey respondents. Otherwise, the recommendation was revised or dropped by the author, based on the anonymous and collated open-ended feedback from the respondents in the survey. If the recommendation or consensus-based statement was revised, the author had the choice to resubmit it to the next round of the survey for voting again by the entire panel. The process was continued until consensus had been reached on each of the presented statement. When the statements that achieved panel consensus had been identified through this process, the executive committee then reviewed each chapter's final recommendations and consensus-based statements to resolve any areas of confusion or inconsistency before a final manuscript was submitted for the peer review process.

### *Review by CHEST and External Reviewers*

When the final manuscript was completed and endorsed by the executive committee, the manuscript underwent peer review process by the organization to consider content, methods, and adherence to the organization's processes. Reviewers were self-nominated and vetted through the same COI disclosure and management process as the panelists. Reviewers were either members of the organization's Cardiovascular and Pulmonary Vascular NetWork, the CHEST GOC, or the CHEST Board of Regents. In addition, CHEST primary reviewers from the GOC and Board of Regents and a reviewer selected by the Editor of the *CHEST* journal reviewed the entire article for fluency and cohesiveness.

## Pharmacologic Therapy for PAH in Adults

Lacking head-to-head comparisons of pharmacologic agents for the treatment of PAH, and because of their differing burdens and risks to patients, we recommend that drug therapy be chosen on the basis of a methodical evaluation of disease severity and the risk for further short-term deterioration. The optimal method of evaluation has not been studied. Despite variability in clinicians' approaches,[7] the WHO FC (Table 2)[18] provides a patient-centered means of assessing disease

**TABLE 2** ] World Health Organization Functional Classification of Patients With Pulmonary Hypertension

| Classification |
|---|
| Class I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope. |
| Class II: Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope. |
| Class III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope. |
| Class IV: Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-sided heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity. |

PH = pulmonary hypertension. Adapted from Rich et al.[18]

impact on a patient's life. Similarly, despite limitations to its use as a surrogate measure, the 6MWD provides functional information. Additionally, hemodynamic, echocardiographic, and laboratory measures (eg, N-terminal brain natriuretic peptide [BNP]) measures provide an assessment of cardiac impairment that may be useful in guiding therapy. A combination of variables, each evaluated in a consistent manner, is recommended. All treatment decisions should be informed by patient preferences, goals, and assessments of health-related quality of life.

**Recommendation**

**1. We suggest that the severity of a PAH patient's disease be evaluated in a systematic and consistent manner, using a combination of WHO FC, exercise capacity, echocardiographic, laboratory and hemodynamic variables in order to inform therapeutic decisions** (Grade CB)**.**

The rarity of PAH makes its recognition and differentiation from other causes of pulmonary hypertension less familiar to most clinicians. Because both an accurate diagnosis and familiarity with the choice of drugs best suited to individual patients are essential to guide therapy, we believe that patients in whom a diagnosis of PAH has been made or is being considered be evaluated at a center with demonstrated expertise and established infrastructure for the management of patients with PAH with advanced disease or complex medical problems. Such evaluations may be difficult because of the distance to such a center, in which case initial telephone consultation between physicians may be a practical approach with plans for in-person evaluation of the patient at the center with advanced PAH expertise as soon as possible. Ongoing care of patients with PAH is best served through close collaboration between locally available physicians and colleagues at centers with advanced expertise in PAH care.

**Recommendations**

**2. We suggest that, whenever possible, all PAH patients be evaluated promptly at a center with expertise in the diagnosis of PAH, ideally prior to the initiation of therapy** (Grade CB)**.**

**3. We suggest collaborative and closely coordinated care of PAH patients involving the expertise of both local physicians and those with expertise in PAH care** (Grade CB)**.**

*Remark:* Appropriate care may require the coordinated efforts of cardiologists, pulmonologists, rheumatologists, primary care, or other specialties.

## Treatment Naive PAH Patients Without Symptoms (WHO FC I) and Patients at Increased Risk for the Development of PAH

Asymptomatic (ie, those with WHO FC I) patients with PAH are rarely identified. Such patients might be identified if screening (ie, the testing of individuals without symptoms) for PH is performed. We lack evidence regarding whether the initiation of PAH-specific treatment is beneficial in patients with WHO FC I symptoms, and no therapy is approved for such use. We believe a careful history is paramount to ensure a true lack of symptoms, as opposed to a patient who has altered his or her activities to accommodate changes in his or her capacities. Asymptomatic patients should be evaluated at regular intervals for the development of symptoms of PAH; the appropriate interval has not been studied. More frequent monitoring (eg, every 3-6 months) may be more appropriate initially until stability has been established. Whether and how often testing should be considered (eg, of exercise capacity or echocardiographic parameters) has similarly not been established.

**Recommendations**

**4. For treatment naive PAH patients with WHO FC I symptoms, we suggest continued monitoring for the development of symptoms that would signal disease progression and warrant the initiation of pharmacotherapy** (Grade CB)**.**

**5. We suggest that patients at risk for the development of PAH (eg, patients with systemic sclerosis or the presence of a known mutation placing the patient at risk for PAH) be monitored for the development of symptoms of PAH** (Grade CB)**.**

Patients with PAH may also have conditions that contribute to the development or worsening of pulmonary hypertension (eg, obstructive sleep apnea or systemic hypertension). These conditions should be optimally treated.

**Recommendation**

**6. We suggest also that contributing causes of PH (eg, sleep apnea and systemic hypertension) in patients with PAH be treated aggressively** (Grade CB)**.**

## Symptomatic Patients With PAH

### *Vasoreactivity Testing and Use of CCBs*

CCBs are a recommended treatment of pulmonary arterial hypertension (PAH) in a defined subset of patients who have a specific biomarker that predicts the

response to therapy. Patients likely to respond to CCBs can be identified by hemodynamic testing with short-acting vasodilators at the time of initial evaluation.[19] No other clinical characteristic or baseline hemodynamic feature predicts those patients who will respond.

**Recommendation**

**7. We suggest that patients with PAH, in the absence of contraindications, should undergo acute vasoreactivity testing using a short-acting agent at a center with experience in the performance and interpretation of vasoreactivity testing** (Grade CB)**.**

*Remark:* Contraindications to acute vasoreactivity testing include a low systemic BP, low CO, or the presence of FC IV symptoms. Acute vasoreactivity testing may be complicated by hypotension, and the misinterpretation of results may result in the inappropriate exposure of patients to the risks of a treatment trial with CCBs without the possibility of clinical benefit. Vasoreactivity testing should be performed by individuals with appropriate training in test performance and interpretation.

The responses to inhaled nitric oxide[20] or intravenously administered acetylcholine,[21] tolazoline,[22] epoprostenol,[23] or adenosine[24] all identify patients with the ability to acutely lower their PAP. The consensus definition of acute vasoreactivity is a fall in mPAP $>$ 10 mm Hg, to an mPAP $<$ 40 mm Hg, with an unchanged or increased CO.[3] Data on long-term clinical benefit (survival out to 5-18 years) come from two large prospective uncontrolled studies.[25,26] It has been reported that approximately 10% of patients with idiopathic PAH (IPAH) who are identified as vasoreactive and treated with high doses of CCBs may manifest a marked reduction in PAP and PVR. True responders to CCBs are uncommon among patients with other forms of PAH (non-IPAH, or PAH occurring in association with underlying disease processes).[27]

High doses of CCBs may be required to realize the full hemodynamic benefit. Although the optimal dose remains uncertain, the typical dosage used is amlodipine 20 to 30 mg/d, nifedipine 180 to 240 mg/d, or diltiazem 720 to 960 mg/d. CCBs at these high dosages are well tolerated, with the major side effect being ankle edema, a known side effect of CCBs, which can be treated with diuretics. CCBs are not specifically approved for use in PAH by either the FDA or European Medicines Agencies.

Patients who respond to CCB therapy show dramatic clinical improvements within the first few months of treatment. It is unknown whether the response to CCBs identifies two subsets of patients with IPAH, different stages of IPAH, or a combination of both. Patients who do not exhibit a marked hemodynamic response to CCBs do not appear to derive similar benefit from their long-term use.

**Recommendation**

**8. We suggest that patients with PAH who, in the absence of right-sided heart failure or contraindications to CCB therapy, demonstrate acute vasoreactivity according to consensus definition, should be considered candidates for a trial of therapy with an oral CCB** (Grade CB)**.**

The use of CCBs in patients with PAH can cause systemic hypotension producing reflex tachycardia, sympathetic stimulation, and right ventricular ischemia. Reports of serious adverse events when CCBs are used inappropriately underscore that CCBs need to be used with caution, and only following testing of a short-acting vasodilator to confirm the presence of vasoreactivity.[28] Their prescription without close patient follow-up or documentation of the beneficial hemodynamic effects is not recommended. Increasing CCB doses in patients who are not vasoreactive can increase morbidity and may be fatal.

**Recommendation**

**9. We suggest that CCBs should not be used empirically to treat PAH in the absence of demonstrated acute vasoreactivity** (Grade CB)**.**

## PAH-Specific Pharmacotherapies

### *Endothelin Receptor Antagonists*

**Bosentan:** Four double-blind placebo-controlled studies of bosentan for the treatment of PAH overall found that bosentan resulted in improvements in exercise capacity, hemodynamics, and time to clinical worsening, with a significantly decreased hazard for hospitalization compared with placebo. The first study enrolled 32 patients with WHO FC III or IV disease due to IPAH or PAH associated with systemic sclerosis.[29] After 12 weeks of treatment, the mean placebo-corrected improvement in 6MWD was 76 m (95% CI, 12-139; $P = .021$) in patients treated with bosentan. In addition, the CI was 1.0 L/min/m$^2$ (95% CI, 0.6-1.4; $P < .0001$) greater in patients given bosentan than in those who received placebo, and the placebo-corrected improvement in PVR was $-415$ dyn/s/cm$^5$ ($-608$ to $-221$, $P = .0002$) in the bosentan group.

A larger RCT of 213 patients had similar entry criteria and found that after 16 weeks of treatment, the 6MWD

among bosentan-treated patients was an average of 44 m greater than patients who had received placebo (95% CI, 21-67 m; $P < .001$). This study included mortality and hospitalization for PH as part of the secondary end point of the number of clinical worsening events, which was defined as the combined end point of death, lung transplantation, hospitalization for pulmonary hypertension, lack of clinical improvement or worsening leading to discontinuation from study drug, need for epoprostenol therapy, or atrial septostomy.[30] Over 28 weeks of follow-up, there were two deaths (3%) in the placebo group, which was not significantly different from the combined bosentan groups (1 [1%] death, hazard ratio [HR] = 0.23; 95% CI, 0.02-2.63). No difference was seen in the combination of hospitalization and worsening PAH, with nine occurrences (13%) in the placebo group compared with six occurrences (4%) in the combined bosentan groups (HR = 0.29; 95% CI, 0.10-0.85).

The third study evaluated bosentan in patients with WHO FC III Eisenmenger syndrome.[31] Fifty-four patients were randomized 2:1 to bosentan (n = 37) or placebo (n = 17) for 16 weeks. Compared with placebo, bosentan decreased PVR index (−472.0 dyn/s/cm$^5$, $P = .04$) and mPAP (−5.5 mm Hg, $P = .04$) and increased 6MWD (53.1 m, $P = .008$).

Finally, the fourth study of bosentan enrolled 185 WHO FC II patients with IPAH, heritable PAH, or PAH associated with HIV infection, anorexigen use, congenital left-to-right cardiac shunts, or connective tissue or autoimmune diseases.[32] Ninety-three patients were randomized to bosentan and 92 to placebo, with 14 (15%) and 15 (16%) patients receiving concomitant sildenafil in each group, respectively. After 6 months, the mean 6MWD (N = 177) increased in the bosentan group (11.2 m; 95% CI, −4.6 to 27.0 m) and decreased in the placebo group (−7.9 m; 95% CI, −24.3 to 8.5); however, the mean treatment effect of 19.1 m (95% CI, 3.6 – 41.8; $P = .08$) did not achieve statistical significance. At month 6, mean PVR (N = 168) was 83.2% (95% CI, 73.8-93.7) of the baseline value in the bosentan group and 107.5% (95% CI, 97.6-118.4) of the baseline value in the placebo group (treatment effect, −22.6%; 95% CI, −33.5 to −10.0; $P < .0001$). The number of clinical worsening events during the course of the trial was a secondary end point in the study and was defined as death from any cause (during the treatment period or as the outcome of a treatment-emergent adverse event that led to permanent discontinuation of study treatment), hospitalization due to PAH complications, or symptomatic progression of PAH. At 6 months, there were no significant differences in death or hospitalizations with one death (1%) in the bosentan group and one death (1%) in the placebo group (HR = 0.99; 95% CI, 0.06-16.05); one patient (1%) in the bosentan group was hospitalized, and three patients (3%) in the placebo group were hospitalized (HR = 0.32; 95% CI, 0.03-3.16).

Adverse events associated with bosentan treatment in these clinical trials included abnormal liver function tests, peripheral edema, palpitations, and chest pain. Monthly monitoring of liver function tests is required for patients receiving bosentan therapy.

**Ambrisentan:** Ambrisentan was evaluated in two concurrent, double-blind, placebo-controlled studies, Ambrisentan in Pulmonary Arterial Hypertension, Randomized Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study (ARIES)-1 and ARIES-2, showing improvement in exercise capacity and time to clinical worsening, although there were no significant differences in death and hospitalization rates compared with placebo.[33] Patients were randomized in a 1:1:1 fashion to placebo, ambrisentan 5 mg, or ambrisentan 10 mg in ARIES-1, and placebo, ambrisentan 2.5 mg, or ambrisentan 5 mg in ARIES-2. These were 12-week studies and included 202 patients in ARIES-1 and 192 in ARIES-2. The patient populations included IPAH, connective tissue disease-associated PAH, HIV-associated PAH, and PAH associated with anorexigen use. Patients in any WHO FC were included in these studies, but the majority of patients were in FC II (ARIES-1: 32%; ARIES-2: 45%) or III (ARIES-1: 58%; ARIES-2: 52%), with only a small percentage of patients in FC I (ARIES-1: 2.5%; ARIES-2: 1.5%) and IV (ARIES-1: 7%; ARIES-2: 2%). The mean placebo-corrected treatment effects were 31 m ($P = .008$) and 51 m ($P < .001$) in ARIES-1 for 5 mg and 10 mg ambrisentan, respectively, and 32 m ($P = .02$) and 59 m ($P < .001$) in ARIES-2 for 2.5 mg and 5 mg ambrisentan, respectively. In 280 patients completing 48 weeks of ambrisentan monotherapy, the improvement in 6MWD was 39 m at week 48 compared with baseline. In the ARIES-1 and ARIES-2 studies,[33] the mean placebo-corrected improvement in 6MWD of all patients studied ranged from 31 to 59 m for the three doses of ambrisentan studied. The range of mean placebo-corrected improvement in 6MWD was nearly identical in WHO FC II and III patients (36-55 m for FC II and 39-45 m for FC III).[33] Clinical worsening events during the trial were defined as the occurrence of death, lung transplantation, hospitalization for PAH, atrial

septostomy, study withdrawal because of the addition of other PAH medications, or early escape criteria. In ARIES-1, there were no significant difference in death or hospitalization rates, with two deaths (3%) in the placebo group and two (1.5%) in the combined ambrisentan group after 12 weeks (HR = 0.49; 95% CI, 0.07-3.55); two hospitalizations (3%) occurred in the placebo group and four (3%) in the combined ambrisentan group (HR = 1.00; 95% CI, 0.18-5.60). In ARIES-2, there was no significant difference in death rates, with three deaths (5%) in the placebo group and two (1.6%) in the combined ambrisentan group after 12 weeks (HR = 0.14; 95% CI, 0.01-2.78); however, nine hospitalizations (14%) occurred in the placebo group, which was significantly more than in the combined ambrisentan group (5 [4%]; HR = 0.26; 95% CI, 0.08-0.80). Peripheral edema, headache, and nasal congestion tended to occur more frequently in patients receiving ambrisentan than placebo, but no patients treated with ambrisentan developed serum aminotransferase concentrations more than three times the upper limit of normal.

**Macitentan:** A multicenter, double-blind, randomized, placebo-controlled, event-driven, phase 3 trial investigated whether long-term treatment with macitentan reduces clinical worsening events among patients with PAH.[34] Patients ≥ 12 years of age who had IPAH or PAH related to connective tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV infection, or drug use or toxin exposure were eligible for inclusion. Confirmation of PAH by right-sided heart catheterization was required, as was a 6MWD ≥ 50 m and WHO FC II, III, or IV. At the time of entry into the study, > 60% of patients were on treatment with oral phosphodiesterase-5 (PDE5) inhibitors, oral or inhaled prostanoids, CCBs, or L-arginine. Patients receiving IV or subcutaneous prostanoids were excluded. Patients were randomly assigned in a 1:1:1 ratio to receive placebo once daily (n = 250), macitentan at a once-daily dose of 3 mg (n = 250), or macitentan at a once-daily dose of 10 mg (n = 242). The composite primary end point was the time from the initiation of treatment to the first event related to PAH (worsening of PAH, initiation of treatment with IV or subcutaneous prostanoids, lung transplantation, or atrial septostomy) or death from any cause up to the end of treatment. Secondary end points included the change from baseline to month 6 in the 6MWD, the percentage of patients with an improvement in WHO FC at month 6, death due to PAH or hospitalization for PAH up to the end of treatment, and death from any cause up to the end of treatment and up to the end of the study. A total of 287 patients had a primary end point event over a median treatment period of 115 weeks: 116 patients (46.4%) in the placebo group, 95 patients (38.0%) in the group that received 3 mg of macitentan, and 76 patients (31.4%) in the group that received 10 mg of macitentan. Worsening of PAH was the most frequent primary end point event. The HR for the primary end point with the 3-mg dose of macitentan vs placebo was 0.70 (97.5% CI, 0.52-0.96; $P = .01$), and the HR with the 10-mg dose of macitentan vs placebo was 0.55 (97.5% CI, 0.39-0.76; $P < .001$). At month 6, the 6MWD had decreased by a mean of 9.4 m in the placebo group and increased by a mean of 7.4 m in the group that received 3 mg of macitentan (treatment effect with 3-mg dose vs placebo, 16.8 m; 97.5% CI, −2.7 to 36.4; $P = .01$) and by a mean of 12.5 m in the group that received 10 mg of macitentan (treatment effect with 10-mg dose vs placebo, 22.0 m; 97.5% CI, 3.2-40.8; $P = .008$). The number of patients in the placebo, 3-mg macitentan, and 10-mg macitentan groups who discontinued the study drug owing to adverse events was 31 (12.4%), 34 (13.6%), and 26 (10.7%), respectively. The incidences of peripheral edema and of alanine aminotransferase or aspartate aminotransferase levels that were more than three times the upper limit of the normal range were similar across the three groups. As compared with patients who received placebo, higher percentages of patients in the two macitentan groups had nasopharyngitis, headache, and anemia. Three patients, one in each group, discontinued treatment because of anemia.

### *Phosphodiesterase Type-5 Inhibitors*

**Sildenafil:** A placebo-controlled study randomized 278 treatment-naive patients to placebo or 20, 40, or 80 mg of sildenafil three times daily for 12 weeks. Patients were predominantly in WHO FC II or III. The primary end point (a placebo-adjusted increase in the 6MWD) was seen with each sildenafil dose, and the drug was approved by the US FDA at the 20 mg tid dose. Improvements in the 6MWD were not statistically different across the dose range studied of 20 to 80 mg tid. Cardiopulmonary hemodynamics were measured at baseline and after 12 weeks of treatment; compared with placebo, mPAP and PVR were lower in patients who received any of the three doses of sildenafil. The proportion of patients who improved at least one WHO FC was significantly greater in each sildenafil treatment group than in the placebo group.[35] Only 7% of patients

treated with placebo improved their FC, compared with 28%, 36%, and 42% of patients treated with 20, 40, and 80 mg tid of sildenafil, respectively. There was no difference observed in the number of clinical worsening events (which were defined as the occurrence of death, transplantation, hospitalization for PAH, or the initiation of additional therapies for PAH).

**Tadalafil:** A placebo-controlled trial randomized 405 patients with PAH to placebo or tadalafil 2.5, 10, 20, or 40 mg once daily for 16 weeks.[36] Approximately one-half of the patients in the study were treatment naive and the other one-half had background therapy with an ETRA that was continued during the study. The primary outcome measure set as a $P < .01$ difference in placebo-adjusted increase in 6MWD after 16 weeks of treatment was met only in patients in the highest-dose treatment group. The mean placebo-corrected increase in 6MWD was 33 m for the combined group of patients receiving 40 mg tadalafil once daily (with and without background ETRA therapy).[36] The mean increases in 6MWD with 40 mg daily was 24 m from baseline among patients in WHO FC I or II and 36 m from baseline among patients in WHO FC III or IV. Data are not available to compare the effect in treatment-naive patients in WHO FCs II and III. There were no differences in the proportions of patients with improved or worsened WHO FC among the tadalafil or placebo groups. There were fewer clinical worsening events among the patients in the 40 mg daily tadalafil group (which were defined as the occurrence of death, heart or lung transplantation, atrial septostomy, hospitalization for PAH or the initiation of new PAH-approved therapy, or worsened WHO FC), predominantly a decrease in number with worsened WHO FC.

### *Prostanoids*

**Epoprostenol:** RCTs of prostanoid therapies in the treatment of PAH are limited. No true double-blind, RCT for IV epoprostenol exists; however, prospective, randomized, controlled, open-label trials support the treatment benefits of this therapy in patients with IPAH[37] as well as in systemic sclerosis-associated PAH.[38] Specifically, in a 12-week, prospective, multicenter, randomized, controlled, open-label trial,[37] continuous IV infusion of epoprostenol plus conventional therapy (including oral vasodilators [CCBs], anticoagulation, diuretic, digoxin, and oxygen) was compared with conventional therapy alone in 81 patients with severe IPAH (WHO FC III or IV). Exercise capacity improved in the 41 patients with epoprostenol (median 6MWD, 362 m at 12 weeks vs 315 m at baseline) and decreased in the 40 patients treated with conventional therapy alone (204 m at 12 weeks vs 270 m at baseline; $P < .002$ for comparison of the treatment groups). Improvement in FC occurred in 16 of 40 patients (40%), worsened in five (13%), and was unchanged in 19 (48%) compared with the conventionally treated group, in which only one patient improved FC (3%), three patients had worsening in their FC (10%), and 27 had no change (87%) over the 12-week trial.[37] There were also improvements in indices of quality of life, hemodynamics, and survival, although those dying in this trial had significantly lower 6MWD at baseline (192 m vs 305 m). A multicenter, randomized, controlled, open-label study[38] of long-term IV epoprostenol treatment in patients with PAH occurring in association with the systemic sclerosis spectrum of disease showed improvement in exercise capacity and hemodynamics. Exercise capacity improved with epoprostenol (median 6MWD, 316 m at 12 weeks compared with 270 m at baseline) but decreased with conventional therapy (192 m at 12 weeks compared with 240 m at baseline). The difference between treatment groups in the median distance walked was 108 m (95% CI, 55.2-180.0 m; $P < .001$). At the end of 12 weeks, 21 patients (38%) improved WHO FC in the group treated with IV epoprostenol, whereas none of the 55 patients receiving conventional therapy improved their WHO FC.[38] Hemodynamics also improved; however, a survival advantage was not demonstrated.

**Treprostinil:** Randomized, placebo-controlled, double-blind trials of IV treprostinil[39] and subcutaneous treprostinil[40] and a nonblinded, placebo-controlled randomized trial of inhaled iloprost have likewise supported treatment benefits in patients with PAH. Specifically, one placebo-controlled, randomized trial of IV treprostinil in treatment-naive PAH FC III and IV patients[39] enrolled 44 study patients with IPAH or familial PAH and randomized them in a 2:1 fashion to either IV treprostinil ($n = 30$) or IV placebo ($n = 14$). Exercise endurance as measured by 6MWD increased in the IV treprostinil-treated patients by a placebo-corrected median of 83 m ($P = .008$) ($326.4 \pm 23$ m from a baseline of $259.2 \pm 11.9$ m in the IV treprostinil arm vs $205.5 \pm 36$ m from a baseline of $231.4 \pm 19.7$ m in the placebo arm). A double-blind, randomized, multicenter, placebo-controlled trial of subcutaneously infused

treprostinil in patients (n = 470) with FC II, III, or IV PAH (IPAH or PAH associated with connective tissue disease or congenital systemic to pulmonary shunts) demonstrated improved exercise capacity as measured by the 6MWD distance (median between treatment group difference, 16 m; $P = .006$).[40] This study also demonstrated improvements in hemodynamics compared with placebo at 12 weeks.[40] Specifically, mean right atrial pressure decreased ($-0.5 \pm 0.4$ mm Hg in subcutaneous treprostinil treated vs $+1.4 \pm 0.3$ mm Hg in placebo treated; $P = .0002$), mPAP decreased ($-2.3 \pm 0.5$ mm Hg vs $+0.7 \pm 0.6$ mm Hg; $P = .0003$), cardiac index increased ($+ 0.12 \pm 0.04$ L/min/m$^2$ vs $-0.6 \pm 0.04$ L/min/m$^2$; $P = .001$), and PVR index decreased ($-3.5 \pm 0.06$ units/m$^2$ vs $+1.2 \pm 0.6$ units/m$^2$; $P = .0001$) in those treated with SC treprostinil compared with placebo. This effect appeared to be dose related.

**Iloprost:** A 3-month, randomized, double-blind, placebo-controlled, multicenter trial of iloprost via inhalation six to nine times per day used a composite primary end point of a 10% improvement in the 6MWD and WHO FC improvement in the absence of clinical deterioration or death.[41] One hundred forty-six patients with PAH and 57 with CTEPH were included. The composite end point was achieved in 17% of treated patients compared with 5% in patients receiving placebo ($P = .007$). The treatment effect on the 6MWD was a mean increase of 36 m in the overall population in favor of iloprost ($P = .004$) and 59 m in the subgroup of 102 patients with IPAH.

Side effects more commonly reported with the use of IV epoprostenol or treprostinil than placebo include headache, jaw pain, diarrhea, abdominal pain, anorexia, vomiting, photosensitivity, cutaneous flushing, and arthralgias.[37-40,42-57] Other adverse effects associated with IV prostanoid use include infection of the catheter site, catheter-related bloodstream infection and sepsis, and malfunction of the drug-delivery system.[37,38,46,47,49,58-63] Site pain occurs frequently in those on subcutaneous treprostinil.[40,64,65] Inhaled prostanoids result in cough, headache, flushing, nausea, and syncope more commonly than placebo with iloprost[41] and cough, headache, and flushing more commonly than placebo with treprostinil.[66]

### *Soluble Guanylate Cyclase Stimulator*

**Riociguat:** A 12-week, double-blind, randomized, placebo-controlled trial of the soluble guanylate cyclase stimulator riociguat was conducted in patients with PAH.[5] The study enrolled 443 patients with symptomatic PAH (idiopathic, familial, or associated with connective tissue disease, congenital heart disease, portal hypertension with liver cirrhosis, or anorexigen or amphetamine use), with a PVR of $> 300$ dyn/s/cm$^5$, an mPAP of $\geq 25$ mm Hg, and a 6MWD of 150 to 450 m. Patients who were receiving no other treatment of PAH and patients who were receiving treatment with ETRAs or prostanoids (excluding IV prostanoids) were eligible; patients who were receiving PDE5 inhibitors were excluded. Oral anticoagulant agents, as well as diuretics and supplemental oxygen at stable doses, were permitted. Patients were randomly assigned, in a 2:4:1 ratio, to one of three regimens: placebo, oral riociguat administered in doses that were individually adjusted for each patient up to 2.5 mg tid, or oral riociguat administered in individually adjusted doses that were capped at 1.5 mg tid. Dose adjustments during the first 8 weeks of the study were made based on the patient's systolic BP (with increases if trough systolic BP was $> 95$ mm Hg) and signs or symptoms of hypotension. The primary end point was the change from baseline in 6MWD. Secondary end points included changes from baseline to the end of week 12 in PVR, N-terminal pro-BNP levels, WHO FC, time to clinical worsening (defined as the occurrence of death, atrial septostomy, heart/lung transplantation, hospitalization for PAH, initiation of new PAH-specific medication or adjustment in prostanoid therapy, or worsening 6MWD or WHO FC), Borg dyspnea score, and quality-of-life assessments. At week 12, the 6MWD had increased from baseline by a mean of 30 m in the 2.5-mg maximum group and had decreased by a mean of 6 m in the placebo group ($P < .001$). Pulmonary vascular resistance decreased by 223 dyn/s/cm$^5$ in the 2.5-mg maximum group, compared with 9 dyn/s/cm$^5$ in the placebo group ($P < .001$). Statistically significant improvements in other hemodynamic variables, including mPAP and CO, were also evident in patients treated with riociguat. Improvements in N-terminal pro-BNP levels, WHO FC, and score on the Borg dyspnea scale were also seen in the riociguat-treated group as compared with placebo, as was a significantly lower incidence of events indicating clinical worsening in the 2.5-mg maximum group than in the placebo group. The most frequently occurring serious adverse events were syncope (in 1% of the patients in the 2.5-mg maximum group vs 4% in the placebo group), worsening pulmonary hypertension (in $< 1\%$ of the patients in the 2.5-mg maximum group vs 2% in the placebo group), chest pain (in 1% of the patients in both

the 2.5-mg maximum group and the placebo group), and right ventricular failure (in 1% of the patients in both groups). Drug-related serious adverse events in the 2.5-mg maximum group included three cases of syncope (in 1% of the patients) and single cases of increased hepatic enzyme levels, dizziness, presyncope, acute renal failure, and hypotension (in a total of 0.4% of the patients).

**Patients With WHO Functional Class II Symptoms:** Direct comparisons of available oral therapies for PAH monotherapy for treatment-naive patients have not been performed, and we do not make recommendations or suggestions of one agent, or class of agent, over another. Three orally active ETRAs (bosentan, ambrisentan, and macitentan), two orally active PDE5 inhibitors (sildenafil and tadalafil), and a single orally active soluble guanylate cyclase stimulator (riociguat) are currently approved for the treatment of PAH in the United States. All six drugs are approved for the treatment of patients with PAH in WHO FC II; however, most of the patients who were enrolled in the pivotal clinical trials that resulted in the approval of these medications were in WHO FC III at the time of study entry. Only about one-third of the patients enrolled into any of these studies were FC II at baseline, and the total number of FC II patients in all of these studies is small. With the exception of a single clinical trial of bosentan,[32] no clinical trial has been designed to specifically examine the effect of treatment on patients with PAH in FC II. As a result, it is uncertain if findings from studies of predominantly WHO FC III patients can be confidently applied to those in FC II. Although emphasizing the limitations of available data and the dangers of comparisons made across studies, the available data suggest that patients with PAH with WHO FC II disease are likely to benefit from treatment with an ETRA, PDE5 inhibitor, or the soluble guanylate cyclase stimulator riociguat. The committee did not believe adequate information is available to permit recommending one agent over another.

ETRAs and PDE5 inhibitors should be initiated at the approved doses. Although the US FDA approved dose of sildenafil for treatment of PAH is 20 mg tid, titration of therapy up to 80 mg tid has been done in clinical trials, and a dose response in hemodynamic response has been noted. For patients who fail to demonstrate and maintain an adequate clinical response to 20 mg sildenafil tid, we recommend consideration of increasing the dose in 20-mg increments to a maximum of 80 mg tid, or adding another agent. Treatment with bosentan > 125 mg bid is associated with greater incidence of transaminase elevation and is not recommended. As treatment with 10 mg of ambrisentan resulted in greater improvement in 6MWD than 5 mg without an observed increase in adverse effects,[33] patients should be started at the 5-mg daily dose of ambrisentan and, if well tolerated and treatment goals have not been reached, the dose should be increased to 10 mg. The dose of riociguat requires dose titration. Based upon currently available evidence showing a risk of systemic hypotension when coadministered with a PDE5 inhibitor, male patients treated with riociguat should also be cautioned not to use PDE5 inhibitors for erectile dysfunction.

**Recommendations**

**For treatment-naive patients with PAH with WHO FC II symptoms who are not candidates for, or who have failed, CCB therapy, we advise monotherapy be initiated with a currently approved ETRA, PDE5 inhibitor, or the soluble guanylate cyclase stimulator riociguat. More specifically in these patients:**

**10. We recommend ambrisentan to improve 6MWD** (Grade 1C)**.**

**11-12. We suggest bosentan to delay time to clinical worsening** (Grade CB) **and improve cardiopulmonary hemodynamics.**

**13. We suggest macitentan to delay the time to clinical worsening** (Grade CB)**.**

**14. We recommend sildenafil to improve 6MWD** (Grade 1C)**.**

**15. We suggest tadalafil to improve 6MWD** (Grade CB)**.**

**16-19. We suggest riociguat to improve 6MWD** (Grade CB)**, improve WHO FC** (Grade CB)**, delay the time to clinical worsening** (Grade CB) **and improve cardiopulmonary hemodynamics.**

Subcutaneous infusion of treprostinil has been approved for the treatment of patients with PAH in FC II; the other parenteral and inhaled prostanoids have not. However, given the considerably greater cost, risks, and administration challenges of drug administration associated with inhaled or continuous-infusion prostacyclin therapy, we do not recommend prostacyclin derivatives as initial therapy for FC II patients. In a similar manner, for patients who remain in FC II on initial PAH therapy, there are no data to support the addition of inhaled or parenteral prostanoid therapy as second-line agents. Prostanoid therapies might be

considered in patients unable to receive oral medications or who have difficulty tolerating, contraindications to, or fail to respond to ETRA or PDE5 inhibitors, or their combination.

**Recommendation**

**20. We suggest that parenteral or inhaled prostanoids not be chosen as initial therapy for treatment naive PAH patients with WHO FC II symptoms or as second line agents for PAH patients with WHO FC II symptoms who have not met their treatment goals** (Grade CB)**.**

**Patients With WHO FC III Symptoms:** Direct comparisons of available oral therapies for PAH monotherapy for treatment-naive patients have not been performed, and we do not make recommendations or suggestions of one agent, or class of agent, over another. ETRAs and PDE5 inhibitors should be initiated at the approved doses. Although the US FDA-approved dose of sildenafil for treatment of PAH is 20 mg tid, titration of therapy up to 80 mg tid has been done in clinical trials and a dose response in hemodynamic response has been noted. In patients who fail to demonstrate and maintain an adequate clinical response to 20 mg sildenafil tid, we recommend consideration of increasing the dose in 20 mg increments to a maximum of 80 mg tid or adding another agent. Treatment with more than the recommended dose of tadalafil (40 mg once daily) has not been studied and is not recommended. Treatment with bosentan > 125 mg bid is associated with greater incidence of transaminase elevation and is not recommended. As treatment with 10 mg of ambrisentan resulted in greater improvement in 6MWD than 5 mg without an observed increase in adverse effects,[33] patients should be started at the 5-mg daily dose of ambrisentan and, if well tolerated and treatment goals have not been reached, increase to the 10-mg dose. The dose of riociguat requires dose titration. Based upon currently available evidence showing a risk of systemic hypotension when coadministered with a PDE5 inhibitor, male patients treated with riociguat should also be cautioned not to use PDE5 inhibitors for erectile dysfunction.

**Recommendations**

**For treatment-naive PAH patients with WHO FC III symptoms who are not candidates for, or who have failed CCB therapy, we advise monotherapy be initiated with a currently approved ETRA, a PDE5 inhibitor, or the soluble guanylate cyclase stimulator riociguat. More specifically in these patients:**

**21. We recommend the use of bosentan to improve 6MWD** (Grade 1B)**.**

**22-23. We suggest the use of bosentan to decrease hospitalizations related to PAH in the short-term** (Grade 2C)**, and to improve cardiopulmonary hemodynamics.**

**24. We recommend the use of ambrisentan to improve 6MWD** (Grade 1C)**.**

**25-26. We suggest macitentan to improve WHO FC** (Grade CB) **and delay the time to clinical worsening** (Grade CB)**.**

**27-29. We recommend the use of sildenafil to improve 6MWD** (Grade 1C) **and to improve WHO FC** (Grade CB)**. We suggest the use of sildenafil to improve cardiopulmonary hemodynamics.**

**30-33. We suggest the use of tadalafil to improve 6MWD** (Grade CB)**, to improve WHO FC** (Grade CB)**, to delay time to clinical worsening** (Grade CB) **and to improve cardiopulmonary hemodynamics.**

**34-37. We suggest riociguat to improve 6MWD** (Grade CB)**, improve WHO FC** (Grade CB)**, delay the time to clinical worsening** (Grade CB) **and improve cardiopulmonary hemodynamics.**

Because of the paucity of comparative effectiveness data among the different agents, none can be definitively recommended preferentially. Inhaled prostanoids (iloprost, treprostinil) have shown less consistent and robust effects than continually infused prostanoid therapy described earlier but may be appropriate initial therapy in select patients with contraindications to oral agents and/or who cannot be treated with continuous parenteral agents. Because of the ease of administration, oral agents are generally preferred as initial therapy unless the patient has more severe symptoms or if there is a worrisome rate of symptom progression, in which case parenteral therapies might be considered. Most clinical data derive from individuals with IPAH, and extrapolation of efficacy may be problematic in other PAH subgroups. In some, such as PAH associated with the systemic sclerosis spectrum of diseases, response to pharmacologic intervention has been studied and generally is less impressive than in patients with IPAH. IV prostanoid therapies require high degrees of patient training, motivation, and support to be successful. IV prostanoid therapies should only be managed by centers with the experience and staffing required to provide 24-h support to complicated patients on these medications. Each of the following parenteral prostanoids has been studied and

approved for use in patients with PAH with WHO FC III symptoms.

**Recommendations**

**For treatment naive PAH patients with WHO FC III symptoms who have evidence of rapid progression of their disease, or other markers of a poor clinical prognosis, we advise consideration of initial treatment with a parenteral prostanoid. More specifically in these patients:**

**38-40. We suggest continuous IV epoprostenol to improve FC** (Grade CB)**, improve 6MWD** (Grade CB)**, and improve cardiopulmonary hemodynamics.**

**41. We suggest continuous IV treprostinil to improve 6MWD** (Grade CB)**.**

**42-43. We suggest continuous subcutaneous treprostinil to improve 6MWD** (Grade CB) **and improve cardiopulmonary hemodynamics.**

Each of the parenteral prostanoids has been studied and approved for use in patients with PAH in WHO FC III. Considering the greater risk, complexity of administration, and cost of parenteral prostanoids, these agents should generally be used as initial therapy for FC III patients who exhibit rapid disease progression or other markers of worse clinical outcomes. They have not generally been adequately studied as up-front combination treatment with oral ETRA or PDE5 inhibitors but may be considered as add-on therapy when patients receiving one or two oral agents fail to meet clinical goals or when they exhibit clinical worsening.

**Recommendations**

**For PAH patients in WHO FC III who have evidence of progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents, we advise consideration of the addition of a parenteral or inhaled prostanoid. More specifically in these patients:**

**44-46. We suggest IV epoprostenol to improve WHO FC** (Grade CB)**, improve 6MWD** (Grade CB)**, and improve cardiopulmonary hemodynamics.**

**47-48. We suggest IV treprostinil to improve 6MWD** (Grade CB) **and improve cardiopulmonary hemodynamics.**

**49. In patients with PAH who remain symptomatic on stable and appropriate doses of an ETRA or a PDE5 inhibitor, we suggest the addition of inhaled treprostinil to improve 6MWD** (Grade 2C)**.**

*Remark:* The usual initial dose of inhaled treprostinil is 3 inhalations (18 μg) every 6 h. However, optimal effect of inhaled treprostinil may require titrating treprostinil doses up to 9 inhalations (54 μg) every 6 h.

**50-51. In patients with PAH who remain symptomatic on stable and appropriate doses of an ETRA or a PDE5 inhibitor, we suggest the addition of inhaled iloprost to improve WHO FC** (Grade CB) **and delay the time to clinical worsening** (Grade CB)**.**

**Patients With WHO FC IV Symptoms:** Most experts in the field consider IV epoprostenol the therapy of choice for WHO FC IV patients based on extensive clinical experience and the findings of improved survival[37] in a single study. Rapid onset of action and titratability of this form of therapy to the severity of the class IV patient's disease make this preferable over oral PAH-specific therapies.

RCT data[39] are limited, but considerable clinical experience supports the exercise benefits of IV treprostinil. Data suggest that this therapy may have a greater risk of catheter-associated infection (with both gram-positive and gram-negative organisms)[59-63] than IV epoprostenol, and it may require higher doses (ng/kg/min) to achieve comparable efficacy.

Prostanoid therapies require patients who are able to manage the complex delivery systems and comply with the therapies to ensure safety. Family support is of paramount importance in the decision to initiate inhaled or infused prostanoid therapy. In addition, prostanoid therapies require proper infrastructure and specialty center care. In centers without the proper infrastructure to ensure safe delivery of these therapies, it is recommended that patients be referred to an experienced pulmonary hypertension center. Severely ill or unstable patients with class IV PAH should be admitted to the hospital for initiation of prostanoid therapy to ensure stabilization and improvement in clinical status and to educate both the patient and family about the safe administration of these therapies to ensure safe transition to outpatient therapy. Listing for lung transplantation should be considered for these patients with WHO FC IV PAH.

**Recommendations**

**For treatment naive PAH patients in WHO FC IV, we advise initiation of monotherapy with a parenteral prostanoid agent. More specifically in these patients:**

**52-54. We suggest continuous IV epoprostenol to improve WHO FC** (Grade CB)**, improve 6MWD**

(Grade CB)**, and improve cardiopulmonary hemodynamics.**

**55. We suggest continuous IV treprostinil to improve 6MWD** (Grade CB)**.**

**56-57. We suggest continuous subcutaneous treprostinil to improve 6MWD** (Grade CB) **and improve cardiopulmonary hemodynamics.**

In general, the magnitude of impact of inhaled prostanoids on these outcomes has been less than that seen with parenteral prostanoid therapy, and these therapies are generally believed to be less optimal in sicker (WHO FC IV) patients. Inhaled iloprost has been studied in patients who remain symptomatic (94% WHO FC III) while receiving a stable dose of bosentan for at least 3 months.[67] Although improvements after 12 weeks in 6MWD, hemodynamics, and time to clinical worsening were observed, the small number of FC IV patients studied makes recommendation of this therapy for these patients tenuous.[67] Inhaled treprostinil has been suggested to sustain 6MWD improvements primarily in WHO FC III patients (on background oral monotherapy), with very limited data for FC IV patients.[68]

Therapy for patients with WHO FC IV status that does not include a prostanoid should be reserved only for those patients unable to safely self-administer or without the social support to handle the rigors of these therapies safely, or in patients who have expressed sufficiently informed preferences to forgo such therapies. FC IV patients who forgo prostanoid therapies must be made aware that transplant centers may not consider them appropriate candidates for lung transplantation. In such patients, some experts would consider up-front initiation of two oral therapies, although supporting evidence is limited.[52]

**Recommendations**

**For treatment naive PAH patients in WHO FC IV who are unable or do not desire to manage parenteral prostanoid therapy, we advise treatment with an inhaled prostanoid in combination with an ETRA. More specifically in these patients:**

**58-59. We suggest bosentan to improve 6MWD** (Grade 2B) **and cardiopulmonary hemodynamics.**

**60-61. We suggest inhaled iloprost to improve 6MWD** (Grade CB)**, and improve WHO FC** (Grade CB)**.**

**62. We suggest inhaled treprostinil (in combination only) to improve 6MWD** (Grade CB)**.**

**Patients With PAH on Established PAH-Specific Therapy:** Treatment with combinations of PAH medications continues to evolve rapidly because of the discovery of multiple biologic pathways for therapeutic intervention and the translation of these discoveries through evidence provided by RCTs. The previous American College of Chest Physicians clinical practice guideline on medical therapy for PAH noted that RCTs studying combination treatments were underway.[2] As of October 1, 2012, investigators have reported five RCTs that compared combination therapy with monotherapy. Four trials compared the addition of a medication or placebo to stable background monotherapy, whereas one small trial compared bosentan against placebo at the time that epoprostenol was initiated. No trial has specifically addressed the important clinical problem of a patient whose deterioration on monotherapy may warrant combination with another pharmacologic class of medication. Major trials of combination therapy are ongoing. One important ongoing trial will provide data to compare initial combination therapy with an ETRA and a PDE5 inhibitor against initial monotherapy with either an ETRA or a PDE5 inhibitor combined with placebo.

**Combination Therapy for the Initial Treatment of Patients With PAH With FC III or IV Symptoms:** One small RCT[47] randomized 33 patients with PAH with WHO FC III or IV symptoms to initiation of IV epoprostenol combined with bosentan or a placebo. The majority of patients were diagnosed with idiopathic PAH (n = 27) or PAH associated with a collagen vascular disease (n = 6). Although both groups showed improved 6MWD, WHO FC, and total pulmonary resistance, there was no significant difference in the primary outcome of change in total pulmonary resistance from baseline to 16 weeks in the epoprostenol/bosentan group vs the epoprostenol/placebo group (mean ± SEM, −36.3% ± 4.3% vs 22.6% ± 6.2%; $P = .08$). There were more serious adverse events observed in the combination therapy group.

**Addition of Inhaled Prostanoid to Stable Oral Monotherapy:** Two prospective double-blind placebo-controlled RCTs compared addition of an inhaled prostanoid against an inhaled placebo in patients with PAH on stable monotherapy with an ETRA or PDE5 inhibitor. The majority of patients were diagnosed with idiopathic PAH or PAH associated with a collagen vascular disease.

One randomized 235 patients with PAH with WHO FC III (98%) or IV symptoms and a 6MWD of 200 to 450 m while treated for at least 3 months with bosentan (70%) or sildenafil (30%) to inhaled treprostinil (≤ 54 μg) or

inhaled placebo four times daily.[66] Inhaled treprostinil improved exercise capacity (placebo-corrected median change from baseline in peak 6MWD of 20 m at week 12; $P < .001$) and quality of life and was safe and well-tolerated. Patients appeared more likely to benefit if the pretreatment 6MWD was < 300 m before the addition of inhaled treprostinil. The usual initial dose of inhaled treprostinil was three inhalations (18 μg) every 6 h. However, the optimal effect of inhaled treprostinil often required titration of treprostinil doses up to nine inhalations (54 μg) every 6 h over a period of 2 weeks.

Another study of 67 patients with PAH who remained symptomatic (94% FC III) despite bosentan therapy randomized participants to inhaled iloprost or placebo.[67] When compared with placebo after 12 weeks, iloprost showed a tendency for improved exercise capacity compared with placebo ($P = .051$) and significant improvement in WHO FC ($P = .002$) and in the occurrence of worsening events ($P = .022$) and was safe and well tolerated.

**Addition of Sildenafil to Stable IV Epoprostenol:** One prospective double-blind placebo-controlled RCT compared the effect of the addition of sildenafil or a placebo in patients with PAH on stable doses of IV epoprostenol (generally between 10 ng/kg/min and 50 ng/kg/min) over 16 weeks.[48] The trial included 267 patients with PAH, most with WHO FC II (25%) or III (65%) symptoms and a 6MWD of 100 to 450 m while treated with stable doses of IV epoprostenol, who had oral sildenafil or placebo added. The majority had idiopathic PAH. The usual initial dose of sildenafil was 20 mg by mouth every 8 h. However, the optimal effect of sildenafil often required titrating sildenafil doses up to 80 mg every 8 h over a period of 8 weeks. Transient changes in epoprostenol dose, typically in increments of 1 to 2 ng/kg/min every 1 to 2 weeks, were made in response to inadequate therapeutic responses.

Compared with placebo, sildenafil was associated with an adjusted treatment difference in 6MWD of +28.8 m (95% CI, 13.9-43.8 m). There were improvements also in hemodynamic measurements and time to clinical worsening. The use of sildenafil in addition to IV epoprostenol was associated with more headaches and dyspepsia. Patients appeared more likely to benefit if the pretreatment 6MWD was > 325 m before the addition of sildenafil.

**Addition of a Long-Acting PDE5 Inhibitor to Stable Background Therapy With an ETRA:** In a 16-week, randomized trial comparing placebo with tadalafil at doses of 2.5, 10, 20, or 40 mg daily, 216 of the 405 patients with PAH were receiving background therapy with bosentan.[36] The placebo-adjusted change in 6MWD in treatment-naive patients was 44 m (n = 186; 95% CI, 20-69; $P = .01$). The average change was 23 m for the 206 on background bosentan therapy who completed the end point 6-min walk (n = 206; 95% CI, 2-48; $P = .09$). Although tadalafil 40 mg daily provided clinical benefit in patients as monotherapy, these data did not support additional benefit of the combination of tadalafil on background bosentan therapy.

Adding a second class of PAH therapy for patients whose clinical status remains unacceptable despite established PAH-specific monotherapy requires that the clinician assess whether the patient has received an adequate trial of the initial monotherapy. At present, this assessment combines evaluation of the duration of monotherapy, the expected response to the monotherapy, the observed response to the monotherapy, and the patient's severity of illness and pace of decline. Unacceptable clinical status will vary for individual patients and clinicians, but symptomatic limitation of desired physical activities usually guide these decisions.

It should be noted that studies adding a second PAH-specific drug to already initiated PAH-specific therapy have routinely continued the initial drug. Published reports have not indicated whether clinical benefit had been noted in response to the initial agent. We lack data to inform whether such practice is appropriate or whether it would be more appropriate to discontinue an initial agent if clinical benefit had not been observed following its initiation. A lack of clinical improvement or a worsening of clinical status with therapy might represent an absence of benefit or even harm from the treatment, progression of disease, or a combination of these factors. As all drugs have potential adverse effects, and PAH-specific therapies are costly, this remains an important gap in the evidence available from clinical trials and a problematic issue for clinical care.

**Recommendations**

**63. In PAH patients initiating therapy with IV epoprostenol, we suggest against the routine simultaneous initiation of bosentan** (Grade CB)**.**

**For WHO FC III or IV PAH patients with unacceptable clinical status despite established PAH-specific monotherapy, we advise addition of a second class of PAH therapy to improve exercise capacity. Such**

**patients are ideally evaluated at centers with expertise in the evaluation and treatment of complex patients with PAH. More specifically:**

**64. In patients with PAH who remain symptomatic on stable doses of an ETRA or a PDE5 inhibitor, we suggest the addition of inhaled iloprost to improve 6MWD** (Grade CB)**.**

**65. In patients with PAH who remain symptomatic on stable doses of an ETRA or a PDE5 inhibitor, we recommend the addition of inhaled treprostinil to improve 6MWD** (Grade 1C)**.**

*Remark:* The usual initial dose of inhaled treprostinil is 3 inhalations (18 μg) every 6 h. However, optimal effect of inhaled treprostinil may require titrating treprostinil doses up to 9 inhalations (54 μg) every 6 h.

**66. In PAH patients who remain symptomatic on stable doses of established IV epoprostenol, we suggest the addition of sildenafil or up titration of epoprostenol to improve 6MWD** (Grade CB)**.**

**67-70. In patients with PAH who remain symptomatic on stable doses of bosentan, ambrisentan or an inhaled prostanoid, we suggest the addition of the soluble guanylate cyclase stimulator riociguat to improve 6MWD** (Grade CB) **WHO FC** (Grade CB) **and cardiopulmonary hemodynamics and to delay the time to clinical worsening** (Grade CB)**.**

**71-73. In patients with PAH who remain symptomatic on stable doses of a PDE5 inhibitor or an inhaled prostanoid we suggest macitentan to improve 6MWD** (Grade CB)**, WHO FC** (Grade CB) **and to delay the time to clinical worsening** (Grade CB)**.**

Data from RCTs are not available to inform the addition of a third pharmacologic class of PAH medication. However, addition of a third class of PAH medication usually indicates poor functional status. In this setting, we believe that treatment with a parenteral prostanoid therapy must be considered.

The recommendations for combination therapy should be used as general guidelines until more is known about which combinations are most efficacious and the optimal timing of combining therapies is available. Until then, an individualized approach should be used by a practitioner who has experience using combination therapy for PAH. In general, escalation of therapy and referral for lung transplantation evaluation should occur when a patient has evidence of disease progression on combination therapy. As noted above, whether established drugs are best continued with the initiation of new agents requires study.

**Recommendation**

**74. For WHO FC III or IV PAH patients with unacceptable or deteriorating clinical status despite established PAH-specific therapy with two classes of PAH pharmacotherapy, we suggest addition of a third class of PAH therapy** (Grade CB)**.**

*Remark:* Such patients are ideally evaluated at centers with expertise in the evaluation and treatment of complex patients with PAH.

## Specific Patient Situations

### *Pregnancy*

Pregnancy was addressed in the 2004 ACCP Medical Therapy Guidelines document.[69] Following is an update to that section of the document. Many patients with PAH are women of childbearing age. The hemodynamic demands of pregnancy are substantial and include an increase of 30% to 50% in blood volume, a similar increase in CO, a 10- to 20-beat/min increase in heart rate, an increase in stroke volume, and decreases in both systemic vascular resistance and BP.[69,70] These hemodynamic changes begin during the first trimester and peak at 20 to 24 weeks of gestation. During labor, there are further increases in CO, and the BP also increases with uterine contractions. Immediately postpartum there are marked volume shifts, with cardiac filling pressures increasing dramatically as a result of decompression of the vena cava and the return of uterine blood into the systemic circulation. The hemodynamic changes associated with pregnancy regress by approximately 6 weeks after delivery. The physiologic changes induced by pregnancy impose a marked hemodynamic stress in women with IPAH, leading to a previously estimated 30% to 50% mortality rate.[71,72] More recent data indicate that the outcome of pregnancy in PAH has improved (a 12% maternal mortality rate was reported in a recent survey[73]), at least when PAH is well controlled. However, pregnancy remains associated with a substantial mortality risk. Because of potential maternal and fetal morbidity and mortality, most experts recommend effective contraception and consideration of early termination if pregnancy occurs in a patient with PAH.[3,74,75]

In addition to the hemodynamic stresses of pregnancy, hormonal changes during and immediately following pregnancy may also be detrimental from a pathophysiologic standpoint. Anecdotal experience suggests that even if a woman successfully delivers a term infant, her pulmonary hypertension may progress during pregnancy and remain worse after pregnancy.

Furthermore, there appears to be an increased incidence of small-for-gestational-age infants born to women with IPAH,[76] as well as an increased incidence of congenital anomalies.

There are several reports of successful treatment of pregnant patients with IPAH with chronic IV epoprostenol,[77-80] inhaled nitric oxide,[81-83] and oral CCBs.[73,84] In general, current management includes early hospitalization for closer monitoring once the fetus is viable, supportive therapy with cautious fluid management, supplemental oxygen, diuretics, and dobutamine, as needed. In addition, the use of a pulmonary artery catheter for close hemodynamic monitoring may be helpful.

Recommendations for the optimal mode of delivery remain controversial; early concerns of high mortality with cesarean section delivery led to an emphasis on vaginal delivery, and a series of seven women with severe pulmonary hypertension who were successfully delivered by the vaginal route has been described.[85] Successful treatment during cesarean section delivery has also been reported, which may partly be due to the changes in the selection and use of anesthetics.[86]

In a meta-analysis of the outcome of pulmonary vascular disease and pregnancy from 1978 through 1996, Weiss and colleagues reported a maternal mortality rate of 36% in Eisenmenger syndrome, 30% in IPAH, and 56% in associated pulmonary hypertension.[72] Similarly, although acknowledging that data on outcomes are limited, previous guidelines from the American Heart Association and the American College of Cardiology recommend that pregnancy be avoided or terminated in women with cyanotic congenital heart disease, pulmonary hypertension, and Eisenmenger syndrome.

**Recommendations**

**75. In patients with PAH, we suggest that pregnancy be avoided** (Grade CB)**.**

*Remark:* Estrogen-containing contraceptives may increase the risk of VTE and are not recommended for women with childbearing potential who have PAH. Additionally, the ETRA bosentan may decrease the efficacy of hormonal contraception. Bosentan, ambrisentan, macitentan and riociguat are contraindicated in pregnancy (category X; evidence of serious fetal abnormalities) and dual mechanical barrier contraceptive techniques are recommended in female patients of childbearing age taking these medications.

**76. When pregnancy does occur in patients with PAH, we suggest care at a pulmonary hypertension center, using a multidisciplinary approach including the pulmonary hypertension, the high-risk obstetrical and cardiovascular anesthesiology services** (Grade CB)**.**

### *Altitude and Air Travel*

We discourage exposure to high altitude (> about 1,829 m [6,000 ft] above sea level), as it may produce hypoxic pulmonary vasoconstriction and further compromise oxygen transport.[87] Supplemental oxygen should be used to maintain saturations > 91% (although firm parameters have not been established in PAH). Air travel can be problematic for patients with PAH, as commercial aircrafts are typically pressurized to the equivalent of approximately 8,000 feet above sea level. High-altitude simulation testing may be useful to more accurately determine the need for and required rate of supplemental oxygen administration during airflight.[88,89]

**Recommendation**

**77. In patients with PAH, we suggest that exposure to high altitude be avoided, and that supplemental oxygen be used as needed during altitude exposure or air travel to maintain oxygen saturations > 91%** (Grade CB)**.**

*Remark*: Patients with borderline oxygen saturations at sea level may require 3-4 L per minute of supplemental oxygen under these conditions, and those already using supplemental oxygen at sea level should increase their oxygen flow rate on commercial aircraft.

### *Vaccinations*

Because of the potentially devastating effects of respiratory infections, immunization against influenza and pneumococcal pneumonia is recommended.

**Recommendation**

**78. In patients with PAH, we suggest maintaining current immunization against influenza and pneumococcal pneumonia** (Grade CB)**.**

### *Surgery*

Invasive procedures and surgery can be associated with increased operative and perioperative risks.[90] Patients with severe PAH are particularly prone to vasovagal events, leading to syncope, cardiopulmonary arrest, and death. Cardiac output is particularly dependent upon heart rate in this situation, and the

bradycardia and systemic vasodilatation accompanying a vasovagal event can result in hypotension. Heart rate should be monitored during invasive procedures, with ready availability of an anticholinergic agent. Oversedation can lead to ventilatory insufficiency and precipitate clinical deterioration. The induction of anesthesia and intubation can be particularly problematic for patients with PAH because it can induce vasovagal events, hypoxemia, hypercarbia, and shifts in intrathoracic pressure-associated changes in cardiac filling pressures. Caution should be used with laparoscopic procedures in which carbon dioxide is used for abdominal insufflation, as absorption can produce hypercarbia, which is a pulmonary vasoconstrictor. Although itself not usually a contraindication to surgery, the potential inhibitory effects of prostanoid drugs on platelet function should be noted.

**Recommendation**

**79. In patients with PAH, we suggest avoiding nonessential surgery, and when surgery is necessary we suggest care at a pulmonary hypertension center, using a multidisciplinary approach including the pulmonary hypertension team, the surgical service, and cardiovascular anesthesiology with careful monitoring and management of clinical status, oxygenation and hemodynamics postoperatively** (Grade CB)**.**

## Conclusions

The options for pharmacotherapy in patients with PAH include several drug classes and delivery routes. The choice of therapy should be made by experienced clinicians and must be based upon an appropriately established diagnosis and evaluation of the patient's disease severity. Available evidence is sufficient to inform a limited number of strong guideline recommendation statements regarding the effect of a specific therapy or combination of therapies on select outcomes in distinct groups of patients defined according to disease severity. Where current evidence is insufficient to inform strong guideline recommendations, expert consensus may provide reasonable advice in evaluating available data and reasonable therapeutic choices. Well-designed studies are needed to compare approaches to therapy in specific groups of patients. As such information and new therapies become available, a reassessment of appropriate clinical advice for the pharmacologic therapy for adult patients with PAH will be required.


## Acknowledgments

**Author contributions:** D. T. was the chairperson of the panel. R. Y. was the GOC liaison. D. T., J. O., L. C., J. R. K., S. L., J. M., H. P., S. R., N. S., E. B. R., T. T., R. Y., C. G. E., and D. B. served as panelists and were on the writing committee for these guidelines.

**Financial/nonfinancial disclosures:** The authors have reported to *CHEST* the following conflicts of interest: Until 2009, Dr Taichman was an employee of the University of Pennsylvania, which received research grant support from Actelion Pharmaceuticals Ltd for participation in the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Registry). He received honoria for CME talks sponsored by the Pulmonary Hypertension Association. Since 2009, he has been an employee of the American College of Physicians. Dr Chung receives grant funding from the Scleroderma Research Foundation. She has received compensation for clinical trial patient enrollment from Gilead; Actelion Pharmaceuticals Ltd; United Therapeutics Corp; Pfizer Inc; MedImmune LLC; Genentech, Inc; and InterMune. She has participated in speaking activities for Actelion Pharmaceuticals Ltd and Gilead and has served on the Advisory Board for Gilead. Dr Lewis is an officer in an institution that probably has a financial relationship with a commercial entity having an interest in the subject of this manuscript. However, the time of working on this manuscript did not overlap with the time she has been employed by this company. She also makes public statements on guideline methodology. Dr Klinger has served as a site investigator for numerous clinical studies in pulmonary hypertension and in numerous pharmacologic, industry-sponsored studies in pulmonary hypertension. Dr Klinger has served as a consultant for Bayer and United Therapeutics Corp. He has served on the steering committee and adjudication committee for industry-sponsored clinical trials. He has received grant support from the National Institutes of Health (NIH) for enrollment of patients in clinical registries. Dr Mandel receives royalties as an author and editor from Elsevier BV and Wolters-Kluwer. Dr Palevsky has within the past 3 years served as a consultant for Actelion Pharmaceuticals Ltd, Bayer AG, Gilead, and United Therapeutics Corp, and has served on data and safety monitoring boards for Aires Therapeutics and Pfizer Inc. He has also served as a grant reviewer for the Entelligence PAH Young Investigators Award Program and has given continuing medical education and other PAH lectures. Dr Rich has received money for speaker's fees from GlaxoSmithKline. Dr Rich has no other intellectual or financial conflicts to disclose. While he had worked in industry in the past, this ended in 2006. Dr Sood has received pharmaceutical grant money for research products and serves as a consultant for advisory board meetings for Actelion Pharmaceuticals Ltd, Bayer AG, Gilead, and United Therapeutics Corp. Dr Rosenzweig has received honoraria from Actelion, Gilead Science, and United Therapeutics as an advisor on Scientific Advisory Board Panels and Ikaria for a study oversight committee in the past three years. Dr Trow has in the distant past served as a consultant for Bayer AG, Actelion Pharmaceuticals Ltd, Gilead, and United Therapeutics Corp. He also used to serve on Speaker's Bureaus for Actelion Pharmaceuticals Ltd, Gilead, and United Therapeutics Corp. No such talks have been given in the 2.5 years prior to this publication. In addition, Dr Trow has served as the primary investigator on the COMPASS (Effects of Combination of Bosentan and Sildenafil vs Sildenafil Monotherapy on Morbidity and Mortality in Symptomatic Patients with PAH) 2 trial and Registry to Prospectively Evaluate Use of Ventavis in Patients With PAH (RESPIRE Registry), which have now finished. Dr Elliott is employed by Intermountain Healthcare (IHC Health Service, Inc) and IHC Health Services, Inc has received compensation trials (on which he is the principal investigator) from Actelion Pharmaceuticals Ltd, Bayer AG, GeNo, Gilead, and United Therapeutics Corp. Dr Elliott serves on the End-Point Adjudication Committee for a study sponsored by Lung LLC. Both he and IHC Health Services received compensation for his service on the End-Point Adjudication Committee. He has received travel and reimbursement for meetings he attended sponsored by Bayer AG, Lung LLC, and Ikaria. He serves as a consultant to Bayer Pharmaceuticals. He received honoria for serving on the REVEAL Steering Committee, which was supported by CoTherix/Actelion. He serves on the board of directors for the Pulmonary Hypertension Association, served on the American College of Chest Physicians Consensus Guidelines

Committee for Pulmonary Arterial Hypertension, and is an advisor for the Scientific Leadership Council of the Pulmonary Hypertension Associations. Dr Badesch has received honoraria for service on steering committees or advisory boards (or as a consultant) to the following companies working in the area of pulmonary hypertension: Actelion Pharmaceuticals Ltd/CoTherix; Gilead; Pfizer Inc; United Therapeutics Corp/Lung Rx; Bayer AG; Ikaria, Inc; and Arena Pharmaceuticals, Inc. He has received grant support for clinical studies from Actelion Pharmaceuticals Ltd/CoTherix; Gilead; Pfizer Inc; United Therapeutics Corp/Lung Rx; Bayer AG; Novartis AG; Ikaria, Inc; and Reata Pharmaceuticals Inc. He provided information pertinent to a legal matter for Actelion Pharmaceuticals, Inc. Mr Ornelas and Dr Yung have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

**Role of sponsors:** This study was funded in total by internal funds from the American College of Chest Physicians.

**Endorsements:** This guideline is endorsed by the Pulmonary Hypertension Association.

**Dedication:** This guideline is dedicated to the memory of our colleague and friend, Dr Robyn Barst, whose commitment to learning how best to treat patients with pulmonary arterial hypertension has been an inspiration.

**Additional information:** The e-Appendix, e-Figure, and e-Tables can be found in the Supplemental Materials section of the online article.

## References

1. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013; 62(suppl 25):D34-D41.
2. Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. *Chest*. 2007; 131(6):1917-1928.
3. McLaughlin VV, Archer SL, Badesch DB, et al; ACCF/AHA. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc, and the Pulmonary Hypertension Association. *Circulation*. 2009;119(16):2250-2294.
4. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol*. 2013; 62(suppl 25):D42-D50.
5. Ghofrani HA, D'Armini AM, Grimminger F, et al; CHEST-1 Study Group. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med*. 2013;369(4):319-329.
6. Kuehn BM. IOM sets out "gold standard" practices for creating guidelines, systematic reviews. *JAMA*. 2011;305(18):1846-1848.
7. Taichman DB, McGoon MD, Harhay MO, et al. Wide variation in clinicians' assessment of New York Heart Association/World Health Organization FC in patients with pulmonary arterial hypertension. *Mayo Clin Proc*. 2009;84(7):586-592.
8. McLaughlin VV. Has the 6-min walk distance run its course? *Chest*. 2012;142(6):1363-1364.
9. McLaughlin VV, Gaine SP, Howard LS, et al. Treatment goals of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(suppl 25): D73-D81.
10. Ivy DD, Abman SH, Barst RJ, et al. Pediatric pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(suppl 25):D117-D126.
11. McCrory DC, Coeytaux RR, Schmit KM, et al. *Pulmonary Arterial Hypertension: Screening, Management, and Treatment*. Rockville, MD: Agency for Healthcare Research and Quality; 2013.
12. Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
13. Atkins D, Best D, Briss PA, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328(7454):1490.
14. Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. *Chest*. 2006;129(1):174-181.
15. Lewis SZ, Diekemper R, Ornelas J, Casey KR. Methodologies for the development of CHEST guidelines and expert panel reports. *Chest*. 2014;146(1):182-192.
16. Fink A, Kosecoff J, Chassin MR, Brook RH. *Consensus Methods: Characteristics and Guidelines for Use*. Santa Monica, CA: RAND Corporation; 1991.
17. Jaeschke R, Guyatt GH, Dellinger P, et al; GRADE Working Group. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. *BMJ*. 2008;337:a744.
18. Rich S. *Primary Pulmonary Hypertension: Executive Summary*. Evian, France: World Health Organization; 1998.
19. Rich S, Kaufmann E. High dose titration of calcium channel blocking agents for primary pulmonary hypertension: guidelines for short-term drug testing. *J Am Coll Cardiol*. 1991;18(5):1323-1327.
20. Atz AM, Adatia I, Lock JE, Wessel DL. Combined effects of nitric oxide and oxygen during acute pulmonary vasodilator testing. *J Am Coll Cardiol*. 1999;33(3):813-819.
21. Dresdale DT, Schultz M, Michtom RJ. Primary pulmonary hypertension. I. Clinical and hemodynamic study. *Am J Med*. 1951; 11(6):686-705.
22. Rudolph AM, Paul MH, Sommer LS, Nadas AS. Effects of tolazoline hydrochloride (priscoline) on circulatory dynamics of patients with pulmonary hypertension. *Am Heart J*. 1958;55(3):424-432.
23. Rubin LJ, Groves BM, Reeves JT, Frosolono M, Handel F, Cato AE. Prostacyclin-induced acute pulmonary vasodilation in primary pulmonary hypertension. *Circulation*. 1982;66(2):334-338.
24. Nootens M, Schrader B, Kaufmann E, Vestal R, Long W, Rich S. Comparative acute effects of adenosine and prostacyclin in primary pulmonary hypertension. *Chest*. 1995;107(1):54-57.
25. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med*. 1992;327(2):76-81.
26. Sitbon O, Humbert M, Jaïs X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation*. 2005;111(23):3105-3111.
27. Montani D, Savale L, Natali D, et al. Long-term response to calcium-channel blockers in non-idiopathic pulmonary arterial hypertension. *Eur Heart J*. 2010;31(15):1898-1907.
28. Packer M, Medina N, Yushak M. Adverse hemodynamic and clinical effects of calcium channel blockade in pulmonary hypertension secondary to obliterative pulmonary vascular disease. *J Am Coll Cardiol*. 1984;4(5):890-901.
29. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet*. 2001;358(9288):1119-1123.
30. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002;346(12): 896-903.
31. Galiè N, Beghetti M, Gatzoulis MA, et al; Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) Investigators. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation*. 2006;114(1):48-54.
32. Galiè N, Rubin Lj, Hoeper M, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet*. 2008;371(9630):2093-2100.
33. Galiè N, Olschewski H, Oudiz RJ, et al; Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies (ARIES) Group. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation*. 2008;117(23):3010-3019.
34. Pulido T, Adzerikho I, Channick RN, et al; SERAPHIN Investigators. Macitentan and morbidity and mortality in

pulmonary arterial hypertension. *N Engl J Med*. 2013;369(9):809-818.

35. Galiè N, Ghofrani HA, Torbicki A, et al; Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005;353(20):2148-2157.
36. Galiè N, Brundage BH, Ghofrani HA, et al; Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension [published correction appears in *Circulation*. 2011;124(10):e279]. *Circulation*. 2009;119(22):2894-2903.
37. Barst RJ, Rubin LJ, Long WA, et al; Primary Pulmonary Hypertension Study Group. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med*. 1996;334(5):296-301.
38. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med*. 2000;132(6):425-434.
39. Hiremath J, Thanikachalam S, Parikh K, et al. Exercise improvement and plasma biomarker changes with intravenous treprostinil therapy for pulmonary arterial hypertension: a placebo-controlled trial. *J Heart Lung Transplant*. 2010;29(2):137-149.
40. Simonneau G, Barst RJ, Galie N, et al; Treprostinil Study Group. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med*. 2002;165(6):800-804.
41. Olschewski H, Simonneau G, Galiè N, et al; Aerosolized Iloprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med*. 2002;347(5):322-329.
42. Jones DK, Higenbottam TW, Wallwork J. Treatment of primary pulmonary hypertension intravenous epoprostenol (prostacyclin). *Br Heart J*. 1987;57(3):270-278.
43. Shapiro SM, Oudiz RJ, Cao T, et al. Primary pulmonary hypertension: improved long-term effects and survival with continuous intravenous epoprostenol infusion. *J Am Coll Cardiol*. 1997;30(2):343-349.
44. Rubin LJ, Mendoza J, Hood M, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. *Ann Intern Med*. 1990;112(7):485-491.
45. Barst RJ, Rubin LJ, McGoon MD, Caldwell EJ, Long WA, Levy PS. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. *Ann Intern Med*. 1994;121(6):409-415.
46. McLaughlin VV, Genthner DE, Panella MM, Rich S. Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med*. 1998;338(5):273-277.
47. Humbert M, Barst RJ, Robbins IM, et al. Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J*. 2004;24(3):353-359.
48. Simonneau G, Rubin LJ, Galiè N, et al; PACES Study Group. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med*. 2008;149(8):521-530.
49. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation*. 2002;106(12):1477-1482.
50. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol*. 2002;40(4):780-788.
51. Badesch DB, McGoon MD, Barst RJ, et al. Long term survival among patients with scleroderma-associated pulmonary arterial hypertension treated with intravenous epoprostenol. *J Rheumatol*. 2009;36(10):2244-2249.
52. Kemp K, Savale L, O'Callaghan DS, et al. Usefulness of first-line combination therapy with epoprostenol and bosentan in pulmonary arterial hypertension: an observational study. *J Heart Lung Transplant*. 2012;31(2):150-158.
53. Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. *Circulation*. 1999;99(14):1858-1865.
54. Aguilar RV, Farber HW. Epoprostenol (prostacyclin) therapy in HIV-associated pulmonary hypertension. *Am J Respir Crit Care Med*. 2000;162(5):1846-1850.
55. Krowka MJ, Frantz RP, McGoon MD, Severson C, Plevak DJ, Wiesner RH. Improvement in pulmonary hemodynamics during intravenous epoprostenol (prostacyclin): A study of 15 patients with moderate to severe portopulmonary hypertension. *Hepatology*. 1999;30(3):641-648.
56. Tapson VF, Gomberg-Maitland M, McLaughlin VV, et al. Safety and efficacy of IV treprostinil for pulmonary arterial hypertension: a prospective, multicenter, open-label, 12-week trial. *Chest*. 2006;129(3):683-688.
57. Gomberg-Maitland M, Tapson VF, Benza RL, et al. Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. *Am J Respir Crit Care Med*. 2005;172(12):1586-1589.
58. Oudiz RJ, Widlitz A, Beckmann XJ, et al. Micrococcus-associated central venous catheter infection in patients with pulmonary arterial hypertension. *Chest*. 2004;126(1):90-94.
59. Centers for Disease Control and Prevention (CDC). Bloodstream infections among patients treated with intravenous epoprostenol or intravenous treprostinil for pulmonary arterial hypertension—seven sites, United States, 2003-2006. *MMWR Morb Mortal Wkly Rep*. 2007;56(8):170-172.
60. Kitterman N, Poms A, Miller DP, Lombardi S, Farber HW, Barst RJ. Bloodstream infections in patients with pulmonary arterial hypertension treated with intravenous prostanoids: insights from the REVEAL REGISTRY(R). *Mayo Clin Proc*. 2012;87(9):825-834.
61. Kallen AJ, Lederman E, Balaji A, et al. Bloodstream infections in patients given treatment with intravenous prostanoids. *Infect Control Hosp Epidemiol*. 2008;29(4):342-349.
62. Rich JD, Glassner C, Wade M, et al. The effect of diluent pH on bloodstream infection rates in patients receiving IV treprostinil for pulmonary arterial hypertension. *Chest*. 2012;141(1):36-42.
63. López-Medrano F, Fernández-Ruiz M, Ruiz-Cano MJ, et al. High incidence of bloodstream infection due to gram-negative bacilli in patients with pulmonary hypertension receiving intravenous treprostinil. *Arch Bronconeumol*. 2012;48(12):443-447.
64. Oudiz RJ, Schilz RJ, Barst RJ, et al; Treprostinil Study Group. Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. *Chest*. 2004;126(2):420-427.
65. Lang I, Gomez-Sanchez M, Kneussl M, et al. Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension. *Chest*. 2006;129(6):1636-1643.
66. McLaughlin VV, Benza RL, Rubin LJ, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol*. 2010;55(18):1915-1922.
67. McLaughlin VV, Oudiz RJ, Frost A, et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2006;174(11):1257-1263.
68. Benza RL, Seeger W, McLaughlin VV, et al. Long-term effects of inhaled treprostinil in patients with pulmonary arterial hypertension: the Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension (TRIUMPH) study open-label extension. *J Heart Lung Transplant*. 2011;30(12):1327-1333.
69. Badesch DB, Abman SH, Ahearn GS, et al. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*. 2004;126(1_suppl):35S-62S.
70. Safdar Z Pulmonary arterial hypertension in pregnant women. *Ther Adv Respir Dis*. 2013;7(1):51-63.
71. McCaffrey RM, Dunn LJ. Primary pulmonary hypertension in pregnancy. *Obstet Gynecol Surv*. 1964;19:567-591.

72. Weiss BM, Zemp L, Seifert B, Hess OM. Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. *J Am Coll Cardiol*. 1998;31(7):1650-1657.

73. Jais X, Olsson KM, Barbera JA, et al. Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. *Eur Respir J*. 40(4):881-885.

74. Elkayam U, Dave R, Bokhari SWH. Primary pulmonary hypertension and pregnancy. In: Elkayam U, Gleicher N, eds. *Cardiac Problems in Pregnancy*. New York, NY: Wiley-Liss; 1998:183-190.

75. Galiè N, Hoeper MM, Humbert M, et al; Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC); European Respiratory Society (ERS); International Society of Heart and Lung Transplantation (ISHLT). Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2009;34(6):1219-1263.

76. Subbaiah M, Kumar S, Roy KK, Sharma JB, Singh N. Pregnancy outcome in women with pulmonary arterial hypertension: single-center experience from India. *Arch Gynecol Obstet*. 2013; 288(2):305-309.

77. Badalian SS, Silverman RK, Aubry RH, Longo J. Twin pregnancy in a woman on long-term epoprostenol therapy for primary pulmonary hypertension. A case report. *J Reprod Med*. 2000;45(2):149-152.

78. Monnery L, Nanson J, Charlton G. Primary pulmonary hypertension in pregnancy; a role for novel vasodilators. *Br J Anaesth*. 2001;87(2): 295-298.

79. O'Hare R, McLoughlin C, Milligan K, McNamee D, Sidhu H. Anaesthesia for caesarean section in the presence of severe primary pulmonary hypertension. *Br J Anaesth*. 1998;81(5):790-792.

80. Stewart R, Tuazon D, Olson G, Duarte AG. Pregnancy and primary pulmonary hypertension: successful outcome with epoprostenol therapy. *Chest*. 2001;119(3):973-975.

81. Decoene C, Bourzoufi K, Moreau D, Narducci F, Crepin F, Krivosic-Horber R. Use of inhaled nitric oxide for emergency Cesarean section in a woman with unexpected primary pulmonary hypertension. *Can J Anaesth*. 2001;48(6):584-587.

82. Lam GK, Stafford RE, Thorp J, Moise KJ Jr, Cairns BA. Inhaled nitric oxide for primary pulmonary hypertension in pregnancy. *Obstet Gynecol*. 2001;98(5 pt 2):895-898.

83. Robinson JN, Banerjee R, Landzberg MJ, Thiet MP. Inhaled nitric oxide therapy in pregnancy complicated by pulmonary hypertension. *Am J Obstet Gynecol*. 1999;180(4):1045-1046.

84. Kiss H, Egarter C, Asseryanis E, Putz D, Kneussl M. Primary pulmonary hypertension in pregnancy: a case report. *Am J Obstet Gynecol*. 1995;172(3):1052-1054.

85. Smedstad KG, Cramb R, Morison DH. Pulmonary hypertension and pregnancy: a series of eight cases. *Can J Anaesth*. 1994;41(6): 502-512.

86. Olofsson C, Bremme K, Forssell G, Ohqvist G. Cesarean section under epidural ropivacaine 0.75% in a parturient with severe pulmonary hypertension. *Acta Anaesthesiol Scand*. 2001;45(2):258-260.

87. Rubin LJ, Badesch DB. Evaluation and management of the patient with pulmonary arterial hypertension. *Ann Intern Med*. 2005;143(4):282-292.

88. Roubinian N, Elliott CG, Barnett CF, et al. Effects of commercial air travel on patients with pulmonary hypertension air travel and pulmonary hypertension. *Chest*. 2012;142(4):885-892.

89. Burns RM, Peacock AJ, Johnson MK, Church AC. Hypoxaemia in patients with pulmonary arterial hypertension during simulated air travel. *Respir Med*. 2013;107(2):298-304.

90. Meyer S, McLaughlin VV, Seyfarth HJ, et al. Outcomes of non-cardiac, nonobstetric surgery in patients with PAH: an international prospective survey. *Eur Respir J*. 2013;41(6):1302-1307.