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Therapy for Pulmonary Arterial Hypertension in Adults

Update of the CHEST Guideline and Expert Panel Report

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BACKGROUND: Pulmonary arterial hypertension (PAH) carries a poor prognosis if not promptly diagnosed and appropriately treated. The development and approval of 14 medications over the last several decades have led to a rapidly evolving approach to therapy, and have necessitated periodic updating of evidence-based treatment guidelines. This guideline statement, which now includes a visual algorithm to enhance its clinical utility, represents the fourth iteration of the American College of Chest Physicians Guideline and Expert Panel Report on Pharmacotherapy for PAH.

METHODS: The guideline panel conducted an updated systematic review to identify studies published after those included in the 2014 guideline. A systematic literature search was conducted using MEDLINE via PubMed and the Cochrane Library. The quality of the body of evidence was assessed for each critical or important outcome of interest using the Grading of Recommendations Assessment, Development and Evaluation approach. Graded recommendations and ungraded consensus-based statements were developed and voted on using a modified Delphi technique to achieve consensus.

RESULTS: Two new recommendations on combination therapy and two ungraded consensus-based statements on palliative care were developed. An evidence-based and consensus-driven treatment algorithm was created to guide the clinician through an organized approach to management, and to direct readers to the appropriate area of the document for more detailed information.

CONCLUSIONS: Therapeutic options for the patient with PAH continue to expand through basic discovery, translational science, and clinical trials. Optimal use of new treatment options requires prompt evaluation at an expert center, utilization of current evidence-based guidelines, and collaborative care using sound clinical judgment.

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KEY WORDS: evidence-based medicine; guidelines; pulmonary arterial hypertension (PAH)

ABBREVIATIONS: 6MWD = 6-min walk distance; AHRQ = Agency for Healthcare Research and Quality; CHEST = American College of Chest Physicians; COI = conflict of interest; ERA = endothelin receptor antagonist; FC = functional class; FDA = Food and Drug Administration; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; HR = hazard ratio; IPAH = idiopathic pulmonary arterial hypertension; MID = minimally important difference; PAH = pulmonary arterial hypertension; PDE5I = phosphodiesterase type-5 inhibitor; PH = pulmonary hypertension; PICO = population, intervention, comparator, outcome; SSc-PAH = scleroderma-spectrum of disease and PAH; SSRI = selective serotonin reuptake inhibitor; WHO = World Health Organization

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Note on Shaded Text: *In this guideline, shaded text with an asterisk (shading appears in PDF only) indicates statements that are newly added or have been changed since the publication of "Pharmacologic Therapy for Pulmonary Arterial Hypertension in Adults: CHEST Guideline and Expert Panel Report" in 2014. Statements that remain unchanged since that edition are not shaded. The order of our presentation should not be interpreted as the guideline panel's order of preference for the use of these agents.*

Summary of Recommendations

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 (Ungraded consensus-based statement).

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 (Ungraded consensus-based statement).

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 (Ungraded consensus-based statement).

Remark: Appropriate care may require the coordinated efforts of cardiologists, pulmonologists, rheumatologists, radiologists, cardiothoracic surgeons, transplant teams, primary care, and other specialists. In addition, appropriate care may involve teams of allied health professionals, including advanced practice clinicians, nurse coordinators, respiratory therapists, exercise physiologists, social workers, pharmacists, among others. Caregiver support, whether it be by family or friends remain an integral part of the care team.

These teams of physicians, and allied health professionals and caregivers are important components in centers with expertise in the diagnosis of PAH.

Remark: Further discussion of tools for evaluating disease severity and mortality risk and description of centers of expertise is provided in the section entitled "Pharmacologic Therapy for PAH in Adults."

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 (Ungraded consensus-based statement).

Remark: Early symptoms concerning for the progression of PAH include new or worsening dyspnea on exertion, fatigue, and weakness. As the disease evolves, symptoms including lower extremity edema, angina or syncope could signal right heart dysfunction and or failure. Patients with PAH and FC I symptoms should be closely monitored for increased symptoms.

5. We suggest that patients at increased risk for the development of PAH (Table 1) **be monitored for the development of symptoms of PAH** (Ungraded consensus-based statement).

6. We suggest also that contributing causes of PH (eg, sleep apnea and systemic hypertension) in patients with PAH be treated aggressively (Ungraded consensus-based statement).

Symptomatic Patients With PAH

Vasoreactivity Testing and Use of Calcium Channel Blockers (CCBs)

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

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interpretation of vasoreactivity testing (Ungraded consensus-based statement).

Remark: Patients at increased risk of adverse events during acute vasoreactivity testing include those with FC IV symptoms, a low systemic BP, low CO, or PVOD. 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.

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 (Ungraded consensus-based statement).

Remark: Careful follow up of these patients is advised. Long-acting nifedipine or diltiazem, or amlodipine are suggested. Due to its potential negative inotropic effects, verapamil should be avoided.[1] The daily doses of these drugs that have shown efficacy in IPAH are relatively high: 120–240 mg for nifedipine, 240–720 mg for diltiazem and up to 20 mg for amlodipine.[2] Patients should be followed up closely for both safety and efficacy, with an initial reassessment after 3 months of therapy. If a patient does not improve to functional class I or II, additional or alternative PAH therapy should be instituted.

Remark: Even though a small percentage (<5%) of PAH in patients with connective tissue diseases may be vasoreactive, there are no studies to suggest that CCB have been effective.

9. We suggest that CCBs should not be used empirically to treat PAH in the absence of demonstrated acute vasoreactivity (Ungraded consensus-based statement).

PAH-Specific Pharmacotherapies

***10. For treatment naive PAH patients with WHO FC II and III, we suggest initial combination therapy with ambrisentan and tadalafil to improve 6MWD** (weak recommendation, moderate quality evidence) (Fig 1).

Patients With WHO FC II Symptoms

For treatment-naive patients with PAH with WHO FC II symptoms who are not candidates for, or who have failed, CCB therapy, we advise that therapy be initiated with a combination of ambrisentan and tadalafil as stated in Recommendation #10. For patients who are unwilling or unable to tolerate combination therapy, we advise monotherapy with a currently approved ERA, PDE5I inhibitor, or the soluble guanylate cyclase stimulator riociguat as outlined in the 2014 guidelines. More specifically in these patients:

11. We recommend ambrisentan to improve 6MWD (strong recommendation, low quality evidence).

12-13. We suggest bosentan to delay time to clinical worsening (Ungraded Consensus-Based Statement).

14. We suggest macitentan to delay the time to clinical worsening (Ungraded Consensus-Based Statement).

15. We recommend sildenafil to improve 6MWD (strong recommendation, low quality evidence).

16. We suggest tadalafil to improve 6MWD (Ungraded Consensus-Based Statement).

17-20. We suggest riociguat to improve 6MWD (Ungraded Consensus-Based Statement)**, improve WHO FC** (Ungraded Consensus-Based Statement)**, delay the time to clinical worsening** (Ungraded Consensus-Based Statement).

21. 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 (Ungraded Consensus-Based Statement).

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 that therapy be initiated with a combination of ambrisentan and tadalafil as stated in Recommendation #10. For patients who are unwilling or unable to tolerate combination therapy, we advise monotherapy with a currently approved ERA, a PDE5I, or the soluble guanylate cyclase stimulator riociguat. More specifically in these patients:

22. We recommend the use of bosentan to improve 6MWD (strong recommendation, moderate quality evidence).

23-24. We suggest the use of bosentan to decrease hospitalizations related to PAH in the short-term (weak recommendation, low quality evidence).

25. We recommend the use of ambrisentan to improve 6MWD (strong recommendation, low quality evidence).

26-27. We suggest macitentan to improve WHO FC (Ungraded Consensus-Based Statement) **and delay the time to clinical worsening** (Ungraded Consensus-Based Statement).

28-30. We recommend the use of sildenafil to improve 6MWD (strong recommendation, low quality evidence)**, to improve WHO FC** (Ungraded Consensus-Based Statement).

31-34. We suggest the use of tadalafil to improve 6MWD (Ungraded Consensus-Based Statement)**, to improve WHO FC** (Ungraded Consensus-Based Statement)**, to delay time to clinical worsening** (Ungraded Consensus-Based Statement).

35-38. We suggest riociguat to improve 6MWD (Ungraded Consensus-Based Statement)**, improve WHO FC** (Ungraded Consensus-Based Statement)**, delay the time to clinical worsening** (Ungraded Consensus-Based Statement).

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:

39-41. We suggest continuous IV epoprostenol to improve FC (Ungraded Consensus-Based Statement)**, improve 6MWD** (Ungraded Consensus-Based Statement).

42. We suggest continuous IV treprostinil to improve 6MWD (Ungraded Consensus-Based Statement).

43-44. We suggest continuous subcutaneous treprostinil to improve 6MWD (Ungraded Consensus-Based Statement).

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:

45-47. We suggest IV epoprostenol to improve WHO FC (Ungraded Consensus-Based Statement)**, improve 6MWD** (Ungraded Consensus-Based Statement).

48-49. We suggest IV treprostinil to improve 6MWD (Ungraded Consensus-Based Statement).

50. In patients with PAH who remain symptomatic on stable and appropriate doses of an ERA or a PDE5I, we suggest the addition of inhaled treprostinil to improve 6MWD (weak recommendation, low quality evidence).

51-52. In patients with PAH who remain symptomatic on stable and appropriate doses of an ERA or a PDE5I, we suggest the addition of inhaled iloprost to improve WHO FC (Ungraded Consensus-Based Statement) **and delay the time to clinical worsening** (Ungraded Consensus-Based Statement).

Patients With WHO FC IV Symptoms

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

53-55. We suggest continuous IV epoprostenol to improve WHO FC (Ungraded Consensus-Based Statement)**, improve 6MWD** (Ungraded Consensus-Based Statement).

56. We suggest continuous IV treprostinil to improve 6MWD (Ungraded Consensus-Based Statement).

57-58. We suggest continuous subcutaneous treprostinil to improve 6MWD (Ungraded Consensus-Based Statement).

59. 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 oral PDE5I and an ERA (Ungraded Consensus-Based Statement).

Remark: The management of PAH patients with FC IV symptoms who are unable or unwilling to use parenteral prostanoid therapy is particularly challenging *because* of their high risk of mortality and the lack of data on the efficacy of oral therapies in this group. Very few FC IV patients were included in trials of oral therapies making it difficult to determine how they will respond. Further studies are needed to determine the efficacy of combination oral and/or inhaled therapies in patients with advanced PAH who are unable or unwilling to tolerate parenteral prostacyclin therapy. Although these guidelines have been limited to pharmacologic therapy for PAH, there is consensus among the panel that the option of lung transplantation should be discussed with

PAH patients who have advanced disease such as FC III who fail to improve on medical therapy or those in FC IV. Patients who are interested in this option should be evaluated at a transplant center experienced in transplantation for patients with PAH.

PAH Patients on Established PAH-Specific Therapy

60. In patients with PAH initiating therapy with IV epoprostenol, we suggest against the routine simultaneous initiation of bosentan (Ungraded Consensus-Based Statement).

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 patients with PAH. More specifically:

61. In patients with PAH who remain symptomatic on stable doses of an ERA or a PDE5I, we suggest the addition of inhaled iloprost to improve 6MWD (Ungraded Consensus-Based Statement).

62. In patients with PAH who remain symptomatic on stable doses of an ERA or a PDE5I, we recommend the addition of inhaled treprostinil to improve 6MWD (strong recommendation, low quality evidence).

63. In patients with PAH who remain symptomatic on stable doses of established IV epoprostenol, we suggest the addition of sildenafil or up titration of epoprostenol to improve 6MWD (Ungraded Consensus-Based Statement).

64-66. 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 (Ungraded Consensus-Based Statement)**, WHO FC** (Ungraded Consensus-Based Statement) **and to delay the time to clinical worsening** (Ungraded Consensus-Based Statement).

67-69. In patients with PAH who remain symptomatic on stable doses of a PDE5I or an inhaled prostanoid we suggest macitentan to improve 6MWD (Ungraded Consensus-Based Statement)**, WHO FC** (Ungraded Consensus-Based Statement) **and to delay the time to clinical worsening** (Ungraded Consensus-Based Statement).

70. 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 (Ungraded Consensus-Based Statement).

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

Combination Studies of Endothelin Receptor Antagonists and Phosphodiesterase Inhibitors

***71. For stable or symptomatic PAH patients on background therapy with ambrisentan, we suggest the addition of tadalafil to improve 6MWD** (weak recommendation, low quality evidence) (Fig 1).

Palliative Care and Supportive Therapies

***72. We suggest incorporating palliative care services in the management of PAH patients** (Ungraded Consensus-Based Statement) (Fig 2).

***73. We suggest that patients with PAH participate in supervised exercise activity as part of the integrated care of their disease** (Ungraded Consensus-Based Statement) (Fig 2).

Preventive Care

74. In patients with PAH, we suggest maintaining current immunization against influenza and pneumococcal pneumonia (Ungraded Consensus-Based Statement).

Specific Patient Situations

Pregnancy

75. In patients with PAH, we suggest that pregnancy be avoided (Ungraded Consensus-Based Statement).

76. When pregnancy does occur in patients with PAH, we suggest care at a pulmonary hypertension center with experience in this area, using a multidisciplinary approach including the pulmonary hypertension, the high-risk obstetrical, and cardiovascular anesthesiology services (Ungraded Consensus-Based Statement).

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 > 91% (Ungraded Consensus-Based Statement).

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

Surgery

78. In patients with PAH, we suggest avoiding non-essential 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 (Ungraded Consensus-Based Statement).

Introduction

World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH) (Table 2)[3,4] is a progressive and fatal disorder for which there was once no effective treatment. However, during the past four decades, basic discoveries and pivotal clinical trials have led to the development and regulatory approval of 14 medications (Table 3).

As a resource for clinicians, the American College of Chest Physicians (CHEST) convened expert panelists who developed guidelines for the treatment of PAH. In 2004, the first guidelines appeared as a supplement to *CHEST*.[5-11] In 2007, a consensus panel updated these guidelines based on evidence published after the 2004 guideline and before September 1, 2006.[1] In 2014, CHEST published the most recent guideline and expert panel report regarding pharmacotherapy for PAH based on evidence available before November 2013.[12]

Since November 2013 investigators have published a substantial body of new evidence related to the treatment of PAH, and two medications received regulatory approval for the treatment of PAH. An orally active preparation of treprostinil was approved by the Food and Drug Administration (FDA) in December 2013 and selexipag, an oral prostacyclin receptor agonist, received FDA approval in 2015. Research groups have provided data on initial treatment with combinations of PAH-targeted medications and data on the addition of PAH medications to background therapy. These new studies and medications have altered the therapeutic landscape for patients with PAH and for the clinicians who care for them.

TABLE 1] Risk for PAH

1. Family history of PAH
2. Known genetic mutation for PAH in patient or first degree relative
a. BMPR2
b. TBXA2
c. KNCK3
d. EIF2AK4
e. Caveolin-1
3. Limited cutaneous scleroderma or mixed connective tissue disease
a. FVC/D_{LCO} > 1.6
b. D_{LCO} < 60%
c. BNP > 2 times normal
4. HIV infection
5. Portal hypertension
6. Exposure to drugs or toxins
a. Fenfluramine/phentermine
b. Aminorex
c. Methamphetamine
d. Dasatinib
7. Congenital heart disease with surgically repaired left to right shunt within 3-6 mo

BNP = brain natriuretic peptide; PAH = pulmonary arterial hypertension.

In January 2016, the CHEST Guidelines Oversight Committee accepted a proposal to update the 2014 guideline and expert panel report, and they organized a broadly constituted guideline and expert panel that included content experts, methodologists, an ethicist, a patient representative, and a pharmacist. The panel followed CHEST's rigorous process for the development of the guidelines in line with the National Academy of Medicine (formerly Institute of Medicine) standards. The panel sought to create a methodologically sound evidence-based document that is credible, accurate, and useful.

Several of the new studies reviewed in this update used a composite of clinical end points indicative of PAH disease progression as the primary outcome. The definition of clinical failure varied between studies, but included events such as death, hospitalization for PAH, clinical worsening based on a decrease in 6-min walk distance (6MWD), change in WHO functional class (FC), or unsatisfactory long-term response. Although these end points were not identical, they represented primary prespecified measures, much like composite scores for recurrent DVT, DVT extension, new

TABLE 2] Comprehensive Clinical Classification of Pulmonary Hypertension

1. PAH
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 *BMPR2*
1.2.2 *ALK-1, ENG, SMAD9, CAV1, KCNK3*
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1′.1 Idiopathic
1′.2 Heritable
1′.2.1 *EIF2AK4* mutation
1′.2.2 Other mutations
1′.3 Drugs, toxins, and radiation induced
1′.4 Associated with:
1′.4.1 Connective tissue disease
1′.4.2 HIV infection
1″. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension because of left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension because of lung diseases and/or hypoxia
3.1 COPD
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4. Chronic thromboembolic pulmonary hypertension
4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
4.2.1 Angiosarcoma
4.2.2 Other intravascular tumors
4.2.3 Arteritis
4.2.4 Congenital pulmonary arteries
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral

See Table 1 legend for expansion of abbreviation. (Adapted with permission from Galie et al[3] and Simonneau et al[4]).

pulmonary embolism, or death from pulmonary embolism were used as a primary end point for clinical trials of antithrombotic therapies in venous thromboembolism.[13,14] The guideline committee recognized the challenges created by the similar but different end points reported in more recent PAH trials and concluded that the small number of studies using composite end points and the differences between the end points made it difficult to determine how to weigh the strength of recommendations. Instead, the guideline committee chose to use the 6-min walk test as a clinically relevant outcome, which allowed data to be extracted from the Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) and Prostacyclin (PGI_2) Receptor Agonist In Pulmonary Arterial Hypertension (GRIPHON) (a clinical trial of a prostacyclin receptor agonist as monotherapy or add-on therapy in patients with PAH) trials. This decision resulted in a weak recommendation with moderate quality of evidence for initial combination therapy with ambrisentan and tadalafil over initial monotherapy with either medication for treatment-naïve patients with FC II or III symptoms (Recommendation 10) and insufficient evidence to make a recommendation for or against the use of selexipag. However, the committee recognizes that some clinicians and patients may place a greater value on slowing PAH disease progression than on improving functional capacity and, if so, may choose to use the beneficial effect of combination therapy or selexipag on delaying time to clinical worsening as their rationale for using these treatments in the management of PAH.

In summary, this article provides current evidence-based guidelines for the treatment of PAH, updating the

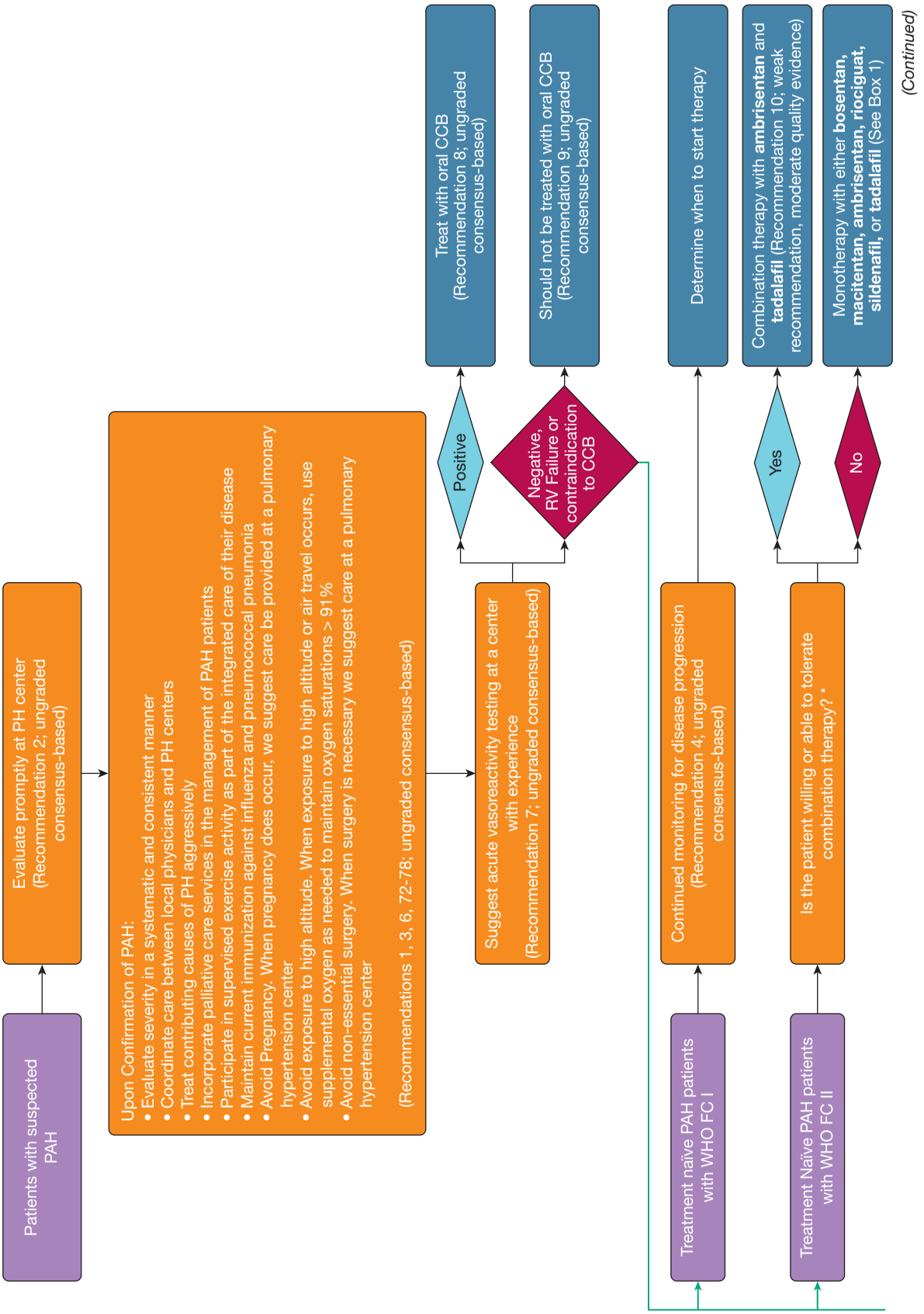
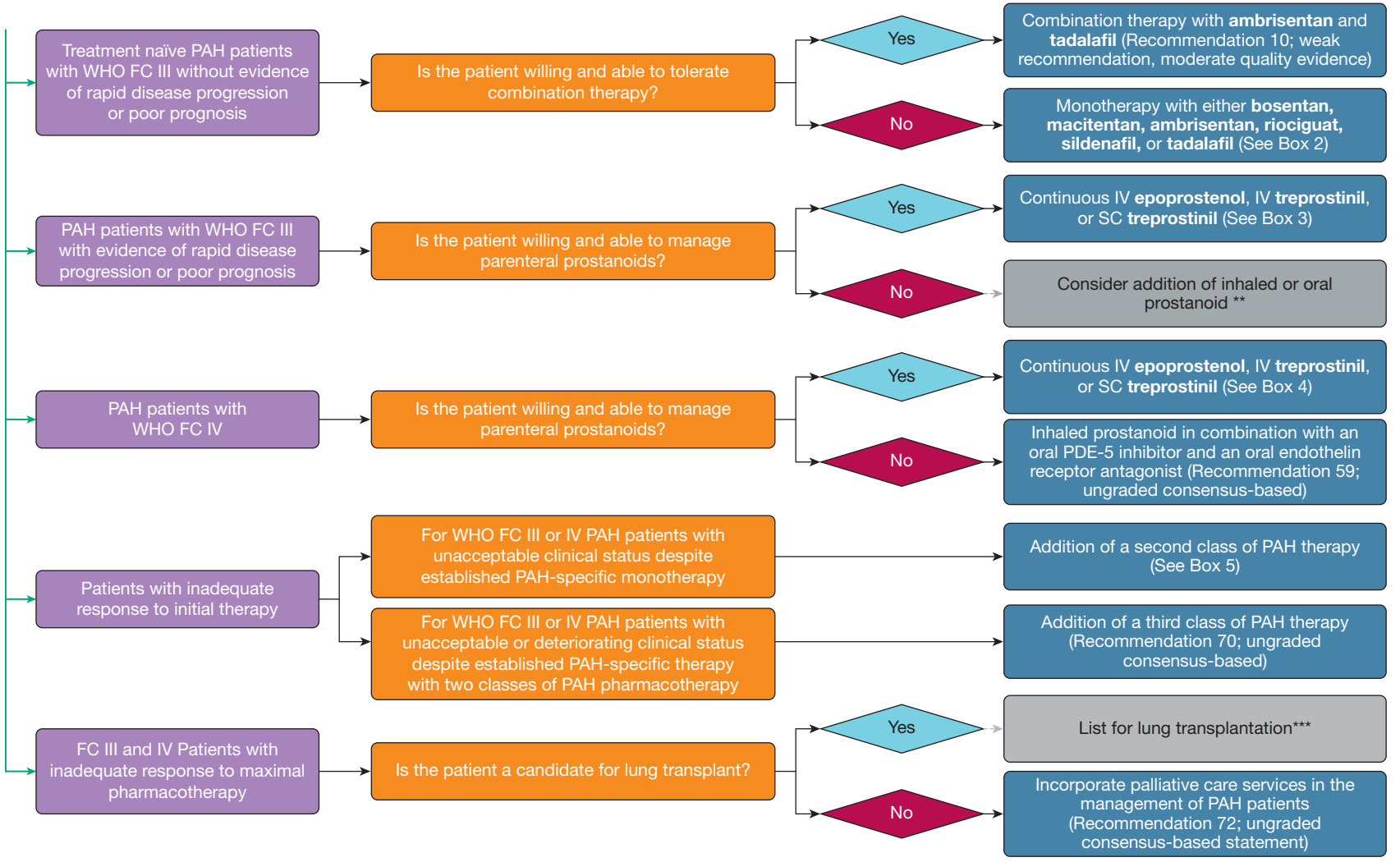


Figure 1 – *Guideline algorithm for pharmacologic therapy for PAH in adults. Where multiple drug options are provided, there is no comparative effectiveness data to suggest greater benefit of one therapy over the other. In these situations, other factors, such as patient preferences & values, cost, and insurance coverage, may guide decision-making. CCB = calcium channel blocker; 6MWD = 6-min walk distance; FC = functional class; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; RV = right ventricular; WHO = World Health Organization.*

Figure 1 – *Continued*



* *Combination therapy carries with it costs as well as multiple medications, including the potential for increased adverse events that may be undesirable for some patients. In these situations patients are unwilling or unable to tolerate combination therapy and the panel suggests monotherapy.*

** *No data available for the use of oral or inhaled prostanoids in patients in whom parental prostanoids are indicated, but patient is unable to comply. Thus, we do not have a specific recommendation for this population*

*** *Lung transplantation is outside the scope of this guideline, which focuses on pharmacotherapy for patients with PAH. Thus, the evidence-based for lung transplants in patients with PAH has not been evaluated by this panel.*

(Continued)

Box 1: Treatment Naïve PAH patients with WHO FC II			
Drug	**Outcome**	**Grade**	**Recommendation Number**
Ambrisentan	Improve 6MWD	strong recommendation, low quality evidence	11
Bosentan	Delay time to clinical worsening	ungraded consensus-based statement	12-13
Macitentan	Delay time to clinical worsening	ungraded consensus-based statement	14
Sildenafil	Improve 6MWD	strong recommendation, low quality evidence	15
Tadalafil	Improve 6MWD	ungraded consensus-based statement	16
Riociguat	Improve 6MWD	ungraded consensus-based statement	17-20
	Improve WHO FC	ungraded consensus-based statement	
	Delay time to clinical worsening	ungraded consensus-based statement	
Parenteral or inhaled prostanoids should not be chosen as initial therapy or as second line agent		ungraded consensus-based	21

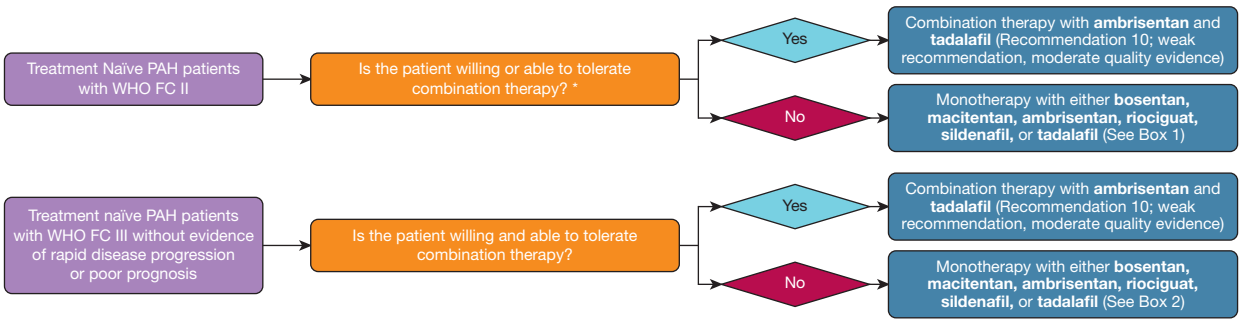
Box 2: Treatment Naïve PAH patients with WHO FC III			
Drug	**Outcome**	**Grade**	**Recommendation Number**
Bosentan	Improve 6MWD	strong recommendation, moderate quality evidence	22
	Decrease hospitalizations related to PAH in the short-term	weak recommendation, low quality evidence	23-24
Ambrisentan	Improve 6MWD	strong recommendation, low quality evidence	25
Macitentan	Improve WHO FC	ungraded consensus-based statement	26-27
	Delay time to clinical worsening	ungraded consensus-based statement	
Sildenafil	Improve 6MWD	strong recommendation, low quality evidence	28-30
	Improve WHO FC	ungraded consensus-based statement	
Tadalafil	Improve 6MWD	ungraded consensus-based statement	31-34
	Improve WHO FC	ungraded consensus-based statement	
	Delay time to clinical worsening	ungraded consensus-based statement	
Riociguat	Improve 6MWD	ungraded consensus-based statement	35-38
	Improve WHO FC	ungraded consensus-based statement	
	Delay time to clinical worsening	ungraded consensus-based statement	

Box 3: PAH patients with WHO FC III with evidence of rapid disease progression or poor prognosis			
Drug	**Outcome**	**Grade**	**Recommendation Number**
Continuous IV epoprostenol	Improve WHO FC	ungraded consensus-based statement	39-41
	Improve 6MWD	ungraded consensus-based statement	
Continuous IV treprostinil	Improve 6MWD	ungraded consensus-based statement	42
Continuous subcutaneous treprostinil	Improve 6MWD	ungraded consensus-based statement	43-44
For patients with continued 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:			
IV epoprostenol	Improve WHO FC	ungraded consensus-based statement	45-47
	Improve 6MWD	ungraded consensus-based statement	
IV treprostinil	Improve 6MWD	ungraded consensus-based statement	48-49
In patients with PAH who remain symptomatic on stable and appropriate doses of an ERA or a PDE5 inhibitor, we suggest the addition of:			
Inhaled treprostinil	Improve 6MWD	weak recommendation, low quality evidence	50
Inhaled iloprost	Improve WHO FC	ungraded consensus-based statement	51-52
	Delay time to clinical worsening	ungraded consensus-based statement	

Box 4: PAH patients with WHO FC IV			
Drug	**Outcome**	**Grade**	**Recommendation Number**
Continuous IV epoprostenol	Improve WHO FC	ungraded consensus-based statement	53-55
	Improve 6MWD	ungraded consensus-based statement	
Continuous IV treprostinil	Improve 6MWD	ungraded consensus-based statement	56
Continuous subcutaneous treprostinil	Improve 6MWD	ungraded consensus-based statement	57-58

Box 5: Patients with inadequate response to initial therapy			
Drug	**Outcome**	**Grade**	**Recommendation Number**
In patients with PAH who remain symptomatic on stable doses of an ERA or a PDE5 inhibitor, we suggest the addition of:			
Inhaled iloprost	Improve 6MWD	ungraded consensus-based statement	61
Inhaled treprostinil	Improve 6MWD	strong recommendation, low quality evidence	62
In patients with PAH who remain symptomatic on stable doses of established IV epoprostenol, we suggest <u>one</u> of the following:			
Addition of sildenafil	Improve 6MWD	ungraded consensus-based statement	63
Up titration of epoprostenol	Improve 6MWD	ungraded consensus-based statement	
In patients with PAH who remain symptomatic on stable doses of bosentan, ambrisentan or an inhaled prostanoid, we suggest the addition of			
Riociguat	Improve 6MWD	ungraded consensus-based statement	64-66
	Improve WHO FC	ungraded consensus-based statement	
	Delay time to clinical worsening	ungraded consensus-based statement	
In patients with PAH who remain symptomatic on stable doses of a PDE5 inhibitor or an inhaled prostanoid we suggest			
Macitentan	Improve 6MWD	ungraded consensus-based statement	67-69
	Improve WHO FC	ungraded consensus-based statement	
	Delay time to clinical worsening	ungraded consensus-based statement	
For stable or symptomatic PAH patients on background therapy with ambrisentan			
Addition of tadalafil	Improve 6MWD	ungraded consensus-based statement	71

Figure 1 – *Continued*



*Combination therapy carries with it costs as well as multiple medications, including the potential for increased adverse events that may be undesirable for some patients. In these situations patients are unwilling or unable to tolerate combination therapy and the panel suggests monotherapy.

Figure 2 – *Combination therapy algorithm. Where multiple drug options are provided, there is no comparative effectiveness data to suggest greater benefit of one therapy over the other. In these situations, other factors, such as patient preferences & values, cost, and insurance coverage, may guide decision-making. See Figure 1 for Boxes 1 and 2. See Figure 1 legend for expansion of abbreviations.*

recommendations that were included in the 2014 guideline and expert panel report. This document reflects CHEST's hybrid approach of accommodating evidence-based recommendations with consensus-based statements in areas where there is insufficient evidence. All clinicians and individuals involved in the care and management of patients with PAH are the target users of this guideline.

Methods

Expert Panel Composition

The qualifications of the suggested cochairs of the guideline were reviewed and approved by CHEST's Professional Standards Committee. Panelists were nominated by the cochairs based on their expertise relative to the scope of the guideline. The complete guideline panel consisted of three cochairs (D. J. L., D. B. B., and J. R. K.), three panelists (G. E., S. M. K., and N. S.), and panel representatives from the following organizations: Pulmonary Hypertension Association (L. D. and E. B. R.), American Thoracic Society (K. F.), American Heart Association (J. J. R.), a representative from CHEST's Guideline Oversight Committee (E. B.), and a patient representative (S. R.).

Conflicts of Interest

All panel nominees were reviewed for their potential conflicts of interest (COIs) by CHEST's Professional Standards Committee. Nominees who were found to have no substantial COIs were approved, whereas nominees with either potential intellectual or financial COIs that were manageable were approved with management. Panelists who were approved with management were prohibited from drafting and voting on recommendations in which they had substantial potential COIs. Additionally, in situations where one of the cochairs had a conflict preventing engagement based on the management terms, an unconflicted cochair led the panel discussion.

As with many rare diseases, PAH has historically lacked research funding from governmental agencies because of the relatively few numbers of patients who would benefit. Patient advocacy organizations' fundraising and public awareness campaigns have until recently provided the bulk of resources for scientific research related to etiology, diagnosis, and treatment of patients with PAH. Similarly, the number of basic science researchers and clinicians involved in the field has been low, yielding a small number of subject matter experts who have been able to conduct clinical trials that have resulted in 14 targeted therapies available within the past 25 years.

Although CHEST's COI protocol clearly limits involvement of guidelines panel members who have potential industry and academic conflicts,[15] the unique circumstances dictated by research in this rare disease presented the option of preparing a document without the expertise of hands-on subject matter experts or involving those with experience and knowledge who also have shared—and gained—their expertise with industry research programs in the effort to improve care for this patient population. As with all CHEST programs, the principals' COI disclosures are published and available to all readers. In an attempt to provide clinicians worldwide with the best evidence analyzed by subject matter experts via its rigid methodologic process, CHEST has chosen to rely on the expertise of panel members who, although having disclosed potential conflicts, are among the small but growing number of experts in this field.

Key Question Development

Key clinical questions were developed using the population, intervention, comparator, outcome (PICO) format. This guideline is an update of the 2014 CHEST guideline, "Pharmacologic Therapy for Pulmonary Arterial Hypertension in Adults: CHEST Guideline and Expert Panel Report."[12] That guideline used the Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Report, "Pulmonary Arterial Hypertension: Screening, Management, and Treatment,"[16] for the evidence review. The guideline specifically focused on key question 3 of that report, which states, "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?" Because this current guideline is an update, the PICO format was developed based on this key question and used the AHRQ methods for defining inclusion and exclusion criteria. The AHRQ methodology did not use composite end points because of the lack of comparability in definition among studies and the assignment of equal importance to events included in the composites such as mortality, hospitalization, transplant, and changes in 6MWD.[16] The panel agreed with this decision and chose to maintain

TABLE 3] Currently Approved Medications for Treatment of Pulmonary Arterial Hypertension

Class	Drug	Route of Administration	Dose
Prostacyclin derivatives	Epoprostenol[a]	IV infusion	2 ng/kg/min Increase as tolerated
	Iloprost	Inhaled	2.5 or 5.0 μg 6-9 inhalations/d
	Treprostinil	Oral	0.25 mg bid or 0.125 mg tid Increase 0.125 mg bid every 3-4 d
		Inhaled	18–54 μg (3-9 inhalations) 4 times daily
		Subcutaneous or IV infusion	1.25 ng/kg/min; increase 1.25 ng/kg/min per week based on clinical response; after week 4 increase by 2.5 ng/kg/min per week based on clinical response
Endothelin receptor antagonists	Bosentan	Oral	125 mg twice daily
	Ambrisentan	Oral	5 or 10 mg once daily
	Macitentan	Oral	10 mg once daily
Phosphodiesterase type-5 inhibitors	Sildenafil	Oral IV injection	20 mg every 8 h
	Tadalafil	Oral	40 mg once daily
Soluble cGMP stimulators	Riociguat	Oral	0.5-1.0 mg every 8 h (increase 0.5 mg every 2 wk as tolerated to maximum dose 2.5 mg)
Prostacyclin receptor agonists	Selexipag	Oral	200 μg twice daily Increase as tolerated to maximum dose of 16,000 μg twice daily

[a]Available in a pH neutral (Flolan) or highly alkaline (Veletri) diluent. The latter provides increased drug stability at room temperature.

the exclusion of composite end points for these reasons and also to maintain consistency between the original and updated review. Among study outcomes, the 6MWD was one of the most frequently reported in studies. The AHRQ evidence review recognized that not all change in 6MWD was clinically important. They used the minimally important difference (MID) specified in PAH literature as 33 m to define clinically significant improvement.[16] We maintained this definition for the review.

During discussion and development of the PICO, the panel decided it was important to update the pharmacologic therapies by adding orally active prostacyclins and prostacyclin receptor agonists and to add nonpharmacologic interventions. Therefore, the final PICO question addressed in this guideline is as follows:

For adult patients with PAH, what are the comparative effectiveness and safety of (1) mono- or combination pharmacotherapies using calcium channel blockers, prostanoids, endothelin antagonists, phosphodiesterase inhibitors, soluble guanylate cyclase stimulators, or orally active prostacyclin derivatives and prostacyclin receptor agonists; (2) cardiopulmonary rehabilitation; (3) palliative care; (4) supportive care; and (5) preventive care on intermediate-term and long-term patient outcomes? (Table 4).

To maintain the integrity of the update process and to add the additional interventions, we decided to manage the evidence review search and selection of eligible studies in two phases. Phase I was an update of the prior review that was conducted by AHRQ, and phase II was a review of the new pharmacologic and nonpharmacologic interventions.

Systematic Literature Search

A systematic literature search for individual studies for this PICO was conducted using the following databases: MEDLINE via PubMed and the Cochrane Library. Searches for phase I were updated from January 2012 to July 2016. The search strategy from the AHRQ review was used with slight modification to focus on Group 1 PAH (e-Table 1). All searches were also limited to English language. Searches for phase II modified the phase I search to retrieve the additional interventions (e-Table 1).

The panelists reviewed the titles and abstracts of the search results independently and in parallel to identify potentially relevant articles based on the inclusion and exclusion criteria (Table 4). All discrepancies were resolved by discussion. Studies deemed eligible then underwent a second round of full-text screening by the same pair of panelists for final inclusion. Again, discrepancies were resolved by discussion. Important data from each included study were then extracted into structured evidence tables completed independently and in parallel by two abstractors.

Quality Assessment

Included studies were assessed for quality and risk of bias using the following assessment tools:

- Documentation and Appraisal Review Tool for systematic review[13]
- Cochrane risk of bias tool for randomized controlled trials[14]
- Risk of bias tool for observational intervention studies[17]

TABLE 4] Population, Intervention, Comparator, Outcome Question

Study Characteristic	Inclusion Criteria	Exclusion Criteria
For adult patients with pulmonary arterial hypertension, what are the comparative effectiveness and safety of (1) mono- or combination pharmacotherapies using calcium channel blockers, prostanoids, endothelin antagonists, phosphodiesterase inhibitors, soluble guanylate cyclase stimulators, or selexipag; (2) cardiopulmonary rehabilitation; (3) palliative care; (4) supportive care; and (5) preventive care on intermediate- and long-term patient outcomes?		
Population	Adult patients with pulmonary arterial hypertension: Group 1 within the pulmonary hypertension World Health Organization clinical classification	Children
Interventions	• Calcium channel blockers (amlodipine, diltiazem, nifedipine) • Prostacyclin derivatives or related (epoprostenol, treprostinil, iloprost) • Endothelin antagonists (bosentan, ambrisentan, macitentan) • Phosphodiesterase inhibitors (sildenafil, tadalafil) • Soluble guanylate cyclase stimulator (riociguat) • Selexipag • Cardiopulmonary rehabilitation • Palliative care • Supportive care (supplemental oxygen, diuretics, digoxin, anticoagulants, physical therapy/rehabilitation) • Preventive care (influenza and pneumonia immunizations, contraception, high-risk pregnancy management, avoiding nonessential surgery and perioperative risk management)	
Comparators	• One pharmacotherapy vs another pharmacotherapy as monotherapy • Monotherapy vs combination therapy, including either as add-on therapy or as an initial treatment regimen using combination therapy • One combination therapy to another combination therapy • Cardiopulmonary rehabilitation vs pharmacotherapy • Cardiopulmonary rehabilitation plus pharmacotherapy vs pharmacotherapy alone • Palliative care vs no palliative care	
Outcomes	• Intermediate-term outcomes (hemodynamic parameters, dyspnea, 6-min walk distance considering MID) • Long-term outcomes (functional class, QoL, right-sided heart failure or right ventricular dysfunction, mortality, PAH-related hospitalization, need for interventional procedures)	Composite end points
Study design	Systematic reviews (with or without, meta-analyses), RCTs, prospective and retrospective cohort studies	

MID = minimally important difference; QoL, quality of life; RCT = randomized controlled trial. See Table 1 legend for expansion of other abbreviation.

Grading the Evidence and Development of Recommendations

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) evidence profiles were created to grade the overall quality of the body of evidence supporting the outcomes for each intervention based on five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The quality of the evidence for each outcome is rated as high, moderate, low, or very low according to GRADE standards.[18,19]

The panel drafted recommendations for each key clinical question that had sufficient evidence. Recommendations were graded using the CHEST grading system (Table 5), based on GRADE, which is composed of two parts: the strength of the recommendation (either strong or weak) and a rating of the overall quality of the body of evidence.[20] In instances where there was insufficient evidence, but a recommendation was still warranted, a weak suggestion was developed and "Ungraded Consensus-Based Statement" replaced the grade. The 2014 guideline used CHEST's previous grading system, modified GRADE. All unchanged recommendations and suggestions from that iteration of the guideline have been converted to standard GRADE format for consistency with current methodology.[21]

The 2014 guideline included multiple ungraded statements referencing use of interventions to improve cardiopulmonary hemodynamic parameters that were not supported by evidence addressing overall patterns of hemodynamic changes. The rationale used at that time was that because only evidence on single parameters (eg, for pulmonary vascular resistance [mean pulmonary artery pressure], cardiac output, cardiac index, right atrial pressure) was available in some circumstances, ungraded statements were included to alert clinicians to when improvements in individual parameters were found. However, because neither GRADE methodology nor the CHEST approach toward consensus statements support ungraded statements in the absence of evidence, all references to potentially improved cardiopulmonary hemodynamic outcomes were removed from this updated guideline when there was a lack of evidence to support such statements.

Consensus Development

All drafted recommendations and suggestions were presented to the panel in an anonymous voting survey to achieve consensus through a modified Delphi technique. Panelists were requested to indicate their level of agreement on each statement, using a 5-point Likert scale derived from the GRADE grid.[20,22] Panelists also had the

TABLE 5] CHEST Grading System

Grade of Recommendation	Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	We are very confident that the true effect lies close to that of the estimate of the effect.	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Strong recommendation, very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa.	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak (conditional) recommendation, high-quality evidence	Benefits closely balanced with risks and burden.	We are very confident that the true effect lies close to that of the estimate of the effect.	The best action may differ depending on circumstances or patients' or societal values. Further research is very unlikely to change our confidence in the estimate of effect.
Weak (conditional) recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden.	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Best action may differ depending on circumstances or patients' or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak (conditional) recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced.	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak (conditional) recommendation, very-low quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced.	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Ungraded consensus-based suggestions			
Ungraded Consensus-Based Statement	Uncertainty because of lack of evidence but expert opinion that benefits outweigh risk and burdens or vice versa.	Insufficient evidence for a graded recommendation.	Future research may well have an important impact on our confidence in the estimate of effect and may change the estimate.

option to provide open-ended feedback on each statement with suggested edits or general comments. According to CHEST policy, each statement required a 75% voting participation rate and at least 80% consensus agreement to be accepted. Panelists with COIs related to the individual statements were not allowed to vote (per the terms of their COI management).

Results

The flowchart in e-Figure 1 presents the results of the systematic search for phase I. The updated search identified 300 potentially new studies. Of those, 106 were selected for full-text review, and of those only four studies met all inclusion criteria.[23-26] Those four studies each examined different combination therapies. Three of the studies earned a low risk of bias rating[23-25]; the fourth earned an unclear rating.[26]

The flowchart in e-Figure 2 presents the results of the systematic search for phase II. The search for new interventions identified 379 citations. Of those, 30 were selected for full-text review, and of those, only 12 studies met all inclusion criteria.[27-38] Of these, two studies evaluated selexipag.[27,28] One systematic review, which included two of the primary studies we identified, evaluated exercise-based rehabilitation.[29] One study evaluated inspiratory muscle training.[30] One systematic review and three primary studies evaluated anticoagulation.[31-34] One study evaluated antiplatelet therapy,[36] and one evaluated selective serotonin reuptake inhibitors (SSRIs).[35] Both systematic reviews were well designed and executed and earned a good quality rating; however, they found little or no evidence relevant to our question. All of the 10 primary studies earned an unclear risk of bias rating.

Pharmacologic Therapy for PAH in Adults

Lacking head-to-head comparisons of pharmacologic agents for the treatment of PAH, and because of their different desirable and undesirable effects for patients, we recommend that drug therapy be chosen based on a methodic evaluation of disease severity, the risk for further short-term deterioration, and the preferences and values of the patient. The optimal method of evaluation has not been studied. Previous guidelines have suggested that WHO FC, echocardiographic assessment of right ventricular function, 6MWD, plasma brain natriuretic peptide or N-terminal pro-brain natriuretic peptide level, hemodynamic measurements, and cardiopulmonary exercise testing in addition to patient symptoms and clinical findings can be useful indicators of disease severity and response to treatment.[39] Specific parameters for each of these variables have been proposed to identify patients at low, intermediate, or high risk of 1-year mortality,[2] and predictive equations for survival in PAH have been developed (Registry to Evaluate Early And Long-term Pulmonary Arterial Hypertension Disease Management [REVEAL], French Pulmonary Hypertension Network predictive equation).[40,41] However, none of these tools have been prospectively validated, and the ability of any of these tools to identify which patients are more likely to derive benefit from a particular therapy has not been formally studied. Lacking data from such studies, we provide recommendations that are based on the WHO FC of the patients enrolled in the clinical studies we evaluated. Please refer to the full treatment algorithm in Figure 3.

Because of the rare occurrence of PAH in the general population, most physicians, including those whose subspecialty practice includes pulmonary and cardiology, are unlikely to encounter sufficient numbers of patients with PAH to gain meaningful experience with the diagnosis and management of this disease. For this reason, we suggest that newly diagnosed patients with PAH be referred to a center with experience in managing PAH, ideally before treatment is initiated. Until recently, there was no formal process for identifying centers that had expertise in managing PAH. In 2015, the Pulmonary Hypertension Association began the PH Care Centers initiative. This program accredits Centers of Comprehensive Care and Regional Clinical Programs in the United States based on their willingness to participate in the program and their ability to demonstrate proficiency in managing patients with PAH. Currently, there are $>$ 50 Pulmonary Hypertension Association (PHA)-accredited centers throughout the United States. Many other centers outside of the PHA accreditation program also have extensive management experience in PAH. Although differences in outcome between patients managed with or without the advice of an expert center have not been formally studied, referral to such centers is recommended by treatment guidelines from the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology and the European Respiratory Society[2] and by the World Symposium on Pulmonary Hypertension. Considering the increased availability of centers that specialize in the management of PAH, the guideline

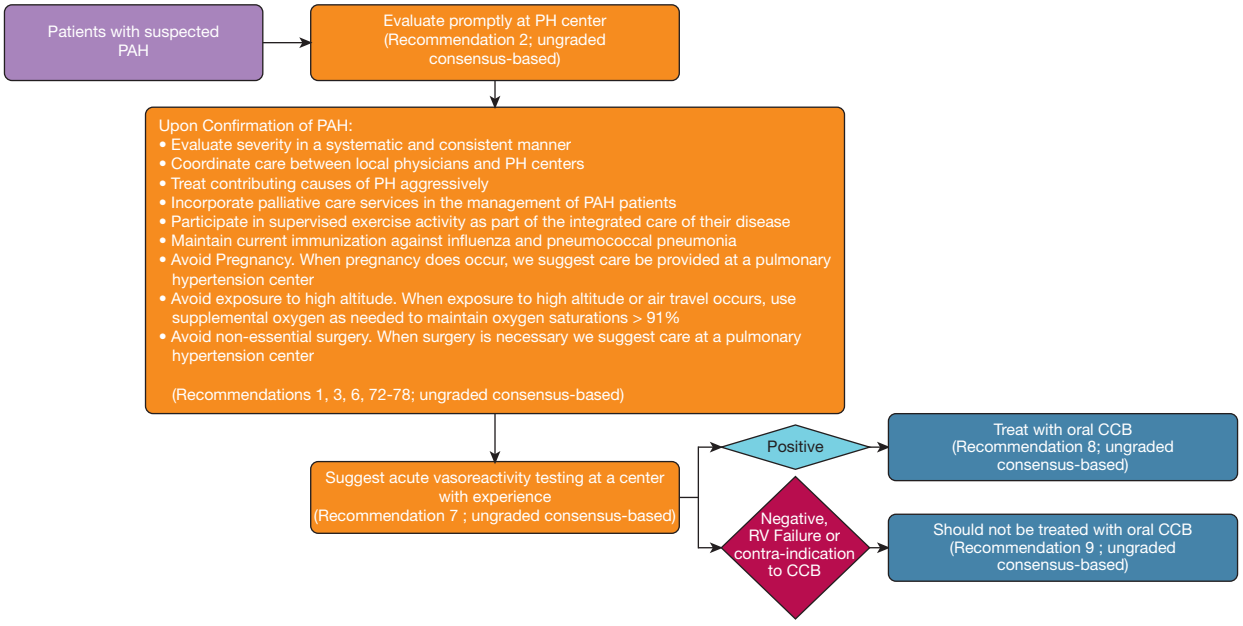


Figure 3 – *General measures algorithm.*

committee agreed that patients should be offered access to these resources whenever feasible.

Despite variability in clinicians' approaches, the WHO FC (Table 6)[42] provides a symptom-based means of assessing disease impact on a patient's life.[43] Similarly, despite limitations in its use as a surrogate measure, the 6MWD provides functional information. Additionally, hemodynamic measurements, echocardiographic assessment, and brain natriuretic peptide or N-terminal pro-brain natriuretic peptide levels 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 and values, goals, and assessments of health-related quality of life.

TABLE 6] World Health Organization Functional Classification of Patients With PH

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 with permission from Rubin et al.[42])

Additionally, the panel acknowledges that the drugs reviewed in this guideline are expensive and that current costs should be taken into account with other information on efficacy, safety, and the patient's individual situation when selecting the most appropriate therapy. Furthermore, multiple drug options are provided for many of the patient conditions. In these circumstances, no comparative effectiveness data are available to suggest greater benefit of one therapy over the other. In these situations, other factors, such as patient preferences and values, cost, and insurance coverage, may guide decision-making.

Newly Approved Therapies

Selexipag: In the first FDA phase 2 trial, 43 adult patients with symptomatic PAH (receiving stable endothelin receptor antagonist [ERA] and/or phosphodiesterase type-5 inhibitor [PDE5I] therapy) were randomized to receive either selexipag or placebo.[27] Dosage was up-titrated in 200-mg increments from 200 mg twice daily on day 1 to the maximum tolerated dose by day 35 (maximum allowed dose of 800 mg twice

daily). Mean change in 6MWD from baseline to 17 weeks was reported as an increase of 24.2 m (95% CI, −23.7 to 72.2 m) for the selexipag group, with no change in 6MWD reported for the placebo group. In this study, the mean difference between the treatment and control groups, and CIs, were not reported. This study was limited by its small size and is described as a "proof of concept" study.

Selexipag was then studied in an FDA phase 3 trial in which 1,156 patients with PAH were randomly assigned to receive placebo or selexipag in individualized doses (maximum dose, 1,600 μg twice daily).[28] The primary end point was a composite of death from any cause or a complication related to PAH up to the end of the treatment period (defined for each patient as 7 days after the date of the last intake of selexipag or placebo). There was no significant difference in PAH mortality (hazard ratio [HR], 0.86; 95% CI, 0.63-1.18; $P = .18$), death from any cause (HR, 0.97; 95% CI, 0.74-1.28; $P = .42$), or absence of worsening in WHO FC (OR, 1.16; 99% CI, 0.81-1.66; $P = .28$) between the two study groups. Although the change in 6MWD within the selexipag group was statistically significant (12 m; 99% CI, 1-24), it did not meet our prespecified MID defined in the PAH literature as 33 m for clinically significant improvement. Because of the use of a composite score as a primary end point and the lack of a clinically relevant change in 6MWD, the committee concluded that there is insufficient evidence at this time to make a recommendation for or against the use of selexipag.

Oral Treprostinil: Oral treprostinil is FDA-approved as monotherapy for PAH. Our updated search identified one randomized controlled trial on monotherapy by Jing et al[44] (FREEDOM-M), which assessed the efficacy and safety of monotherapy with oral treprostinil compared with placebo. Investigators found that among patients receiving oral treprostinil, 6MWD significantly improved at 8 weeks (17 m; 95% CI, 1-33 m; $P = .0307$) and 12 weeks (23 m; 95% CI, 4-41 m; $P = .0125$). This study was ultimately excluded from our review because of the inclusion of pediatric patients (≥ 12 years of age); therefore, the panel was unable to make a recommendation for or against the use of oral treprostinil as monotherapy.

There is also currently no evidence to support its use in add-on or combination therapeutic approaches, as subsequently discussed in the Combination of Prostacyclin Therapy with ERAs and PDE5Is section.

Combination Trials in PAH Since 2014

Since the 2014 guidelines were published, four studies have been completed in which PAH-specific therapies have been used in combination, resulting in some changes and additions to the previous recommendations.[23-26]

Combination Studies of ERAs and Phosphodiesterase Inhibitors: Since the 2014 guidelines, three studies have been published using combinations of ERAs and PDE5Is in different scenarios.

Bosentan Added to Sildenafil Therapy in Patients With PAH: McLaughlin et al[24] conducted a multicenter prospective, double-blind, event-driven trial of patients with symptomatic PAH who were on stable therapy with sildenafil at ≥ 20 mg three times daily for at least 3 months. Three hundred and thirty-four patients were randomized to receive placebo or bosentan at 62.5 mg twice daily for 1 month followed by 125 mg twice daily. The between-group mean difference for 6MWD was found to be 21.8 m (95% CI, 5.9-37.8; $P = .0106$) in the bosentan-treated patients compared with placebo. Although this increase was found to be statistically significant, it was less than the MID (33 m) identified in the methodology section of this guideline. No differences between the two groups were identified in other outcomes of interest (change in WHO FC or time to death from any cause). There is currently insufficient evidence to make a recommendation for or against the addition of bosentan to patients on sildenafil.

Initial Use of Ambrisentan Plus Tadalafil in PAH: In the Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial, Galie et al[23] studied combination therapy with ambrisentan (10 mg daily) plus tadalafil (40 mg daily) vs either ambrisentan or tadalafil alone in PAH.

A total of 610 patients were randomized 2:1:1 to receive ambrisentan (10 mg daily) plus tadalafil (40 mg daily) vs ambrisentan plus placebo vs tadalafil plus placebo, respectively. The primary outcome was the time to first event of clinical failure defined as the composite end point for death, hospitalization for worsening PAH (including transplant, atrial septostomy, and initiation of parenteral prostanoid therapy), disease progression (defined as a 15% decrease in the 6MWD combined with a FC III or IV at two consecutive visits separated by 14 days), or unsatisfactory long-term clinical response in patients completing at least 6 months of the trial (assessed as a decrease in 6MWD from baseline and FC III symptoms at two visits separated by at least 6 months).

The median change from baseline for 6MWD improved more in the combination treatment group than the pooled monotherapy groups (49 vs 24 m, respectively; $P < .001$) (e-Table 2). There was no effect on the WHO FC. The improvement in 6MWD in the treatment group suggests that initial combination treatment may be more efficacious than monotherapy in improving exercise capacity. Because there was only one study, and the clinical outcome measured demonstrated a borderline clinically significant effect on 6MWD, the panel supported a weak suggestion instead of a strong recommendation. It is important that each physician and patient work together to decide best treatment options based on each individual situation and what is in the best interest for the particular patient.

Recommendation: *10. For treatment naive PAH patients with WHO FC II and III, we suggest initial combination therapy with ambrisentan and tadalafil to improve 6MWD (weak recommendation, moderate quality evidence).

Randomized Study of Adding Tadalafil to Existing Ambrisentan in PAH: Zhuang et al[26] conducted a prospective, double-blinded, randomized controlled study to investigate the efficacy of the addition of oral tadalafil in patients receiving background ambrisentan therapy for PAH. One hundred and twenty-four patients with symptomatic idiopathic pulmonary arterial hypertension (IPAH), heritable PAH, or PAH associated with connective tissue disease; anorexigen use; or repaired congenital heart disease who were treated with ambrisentan (10 mg daily) for ≥ 4 months received either placebo or tadalafil (40 mg daily) for 16 weeks.

At 16 weeks, there was a nonsignificant improvement in 6MWD from baseline in the placebo group (mean change, 18.3 m; 95% CI, 4.3-34.8; P = not significant) and a significant improvement in the tadalafil group (mean change, 54.4 m; 95% CI, 30.2-80.1; $P < .05$) (e-Table 3). Compared with the placebo group, the increase in the treatment group was found to be significant ($P = .042$), but the mean difference between the treatment group and control group, and CIs, were not reported. Change in WHO FC did not differ between groups at 16 weeks. Because there was only one study, and the clinical outcome measured demonstrated a borderline clinically significant effect on 6MWD, the panel supported a weak suggestion instead of a strong recommendation. It is still important that each physician and patient work together to decide best treatment options based on each individual situation and what is in the best interest for the particular patient.

Recommendation: *71. For stable or symptomatic PAH patients on background therapy with ambrisentan, we suggest the addition of tadalafil to improve 6MWD (weak recommendation, low quality evidence).

Combination of Prostacyclin Therapy With ERAs and PDE5Is: Since publication of the 2014 guidelines, oral treprostinil was approved for treatment of PAH. Two studies examined the effect of the addition of oral treprostinil to background ERAs and/or PDE5Is.[25]

Tapson et al[25] performed an international multicenter, double-blind, placebo controlled trial of the addition of oral treprostinil to patients with PAH receiving background therapy with ERAs and/or PDE5Is in the FREEDOM-C2 trial. No significant difference was shown in the primary outcome of improvement in the 6MWD from baseline to 16 weeks (median difference, 10 m; 95% CI, −2 to 22 m; $P = .089$).

This study is limited by a high percentage of premature discontinuations, relatively short treatment duration, relatively small size, and potential ceiling effect of the 6MWD in patients already receiving multiple background therapies.

At this time, there is insufficient evidence to make a recommendation for or against the addition of bid oral treprostinil to patients on background therapy with ERAs and/or PDE5Is.

Additional Considerations for Combination Therapies in PAH: As discussed in the 2014 guidelines and previously reviewed, the addition of therapies to existing treatments or the use of multiple therapies as initial treatment remains a complicated issue. Consideration of the addition of new therapies to a patient already on PAH treatment requires that the clinician assess whether the patient has received an adequate trial of the initial therapy to assess efficacy and clinical status. This assessment includes evaluation of the duration of therapy, the expected response to the therapy, the observed response to the therapy, 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 guides these decisions. The clinician must then review the evidence available to determine which additional therapy is likely to benefit the patient the most while limiting expected adverse

events. The studies reviewed here represent the increasing interest in assessing combination therapy in additive or initial strategies and provide some framework to aid the clinician in these decisions.

As identified in the 2014 guidelines, studies adding a second PAH-specific drug to already initiated PAH-specific therapy have routinely continued the initial drug. None of the studies reviewed here indicate that the patient has or has not had a therapeutic benefit of the initial treatment but instead state the patients are stable. Published reports have not indicated whether clinical benefit had been noted in response to the initial agent. Indeed, many authors cite the potential ceiling effect of background treatments on outcome measures as limitations to identifying a benefit of their intervention, but fail to provide enough clinical information to make that determination. We continue to 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 after its initiation, as was done in a recently published open-label study for riociguat.[45] 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. Because 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. More combination studies may inform clinicians to potential additive or even synergistic effects in the future.

Palliative Care and Supportive Therapies

Six studies were identified for palliative care and supportive therapies. After full-text review, no eligible studies on palliative care and PAH exist to provide direct recommendations. The studies relating to supportive care measures included four on anticoagulation,[31-34] one on antiplatelet therapy,[36] and one on SSRI additions.[35]

Palliative Care: Palliative medicine is a well-established and growing field with clearly documented benefits to patients and outcomes. Other lung diseases such as lung cancer have shown significant improvements in outcome measurements with the addition of palliative care to standard interventions. Our search identified no eligible studies to directly evaluate the effectiveness of palliative care therapies in conjunction with standard interventions for PAH, but this lack of evidence in the literature does not negate the potential benefits palliative care offers to all patients and families for assisting in management of disease burden, pain, and symptoms of chronic or acute needs. The addition of palliative care interventions to assist in management of disease burden and symptoms can often be beneficial to improving patient quality of life.

Recommendation: *72. We suggest incorporating palliative care services in the management of PAH patients (Ungraded Consensus-Based Statement).

Pulmonary Rehabilitation: Pulmonary rehabilitation has been shown to be safe and beneficial in improving exercise capacity and quality of life in chronic lung disease (ie, COPD, lung cancer, pulmonary fibrosis).[46-48] Studies exist on many aspects related to supervised exercise-based rehabilitation in pulmonary hypertension (PH).[49-52] International guidelines recommend integrating exercise training into the care of patients with PAH.[2] Pulmonary rehabilitation, however, was not evaluated as a therapy for PAH in the 2014 CHEST guidelines. For this iteration of the CHEST guidelines, no studies were identified in our review that directly addressed pulmonary rehabilitation in adults with PAH.

Exercise Training: Our search identified three studies that assessed exercise training in PH.[29,37,38] The studies by Ehlken et al[38] and Weinstein et al[37] were included in a full systematic review by Morris et al.[29] To avoid double counting, we used the systematic review only. Although the systematic review included other studies on PH, only two small studies (totaling 36 patients combined) were specific to patients with Group 1 PAH and were of low quality (e-Table 4).

Profile Inspiratory Muscle Training: One small study by Saglam et al[30] met our inclusion criteria. Twenty-nine clinically stable patients with PAH were randomly assigned to inspiratory muscle training program or to a sham protocol. After 6 weeks, a significant change in 6MWD was seen in the inspiratory muscle training group (426.93 $\pm$ 97.76 before and 476.43 $\pm$ 90.11 after; $P = .001$), and no significant change was seen in the control group (357.24 $\pm$ 137.17 before and 334.00 $\pm$ 121.60 after; $P = .109$) (e-Table 5). The difference between groups was found to be significant ($P < .001$), but it is unclear if this difference is because of group differences at the start of the study.

Recommendation: *73. We suggest that patients with PAH participate in supervised exercise activity as part of the integrated care of their disease (Ungraded Consensus-Based Statement).

Anticoagulation: Four studies were identified in our review addressing anticoagulation.[31-34] The Ezedunukwe et al systematic review[31] evaluated randomized controlled trials that addressed the effectiveness and potential adverse events of anticoagulation in the management of PH. No eligible studies were identified in this review. Olsson et al[32] conducted a retrospective cohort analysis from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry. Among patients with IPAH on any type of anticoagulant, the adjusted HR for survival was found to be 0.79 (95% CI, 0.66-0.94; $P = .007$). For patients with the scleroderma-spectrum of disease and PAH (SSc-PAH), the use of anticoagulants was associated with a trend toward worse survival (HR, 1.82; 95% CI, 0.94-3.54; $P = .08$).

Preston et al[33] also conducted a retrospective cohort analysis using data from the Registry to Evaluate Early And Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) registry to assess the effect of warfarin anticoagulation on survival in IPAH and SSc-PAH. In patients with IPAH, warfarin use was not significantly associated with survival (adjusted HR, 1.37; 95% CI, 0.84-2.25; $P = .17$). Likewise, in patients with SSc-PAH, warfarin use was also not significantly associated with better survival (adjusted HR, 1.60; 95% CI, 0.84-3.06; $P = .15$).

The Kang et al study[34] also assessed survival outcomes associated with the use of warfarin among Korean patients with IPAH. They found that among the 31 included patients, warfarin use was associated with better survival outcomes (HR, 0.21; 95% CI, 0.045-0.976; $P = .047$).

These included studies could not be combined in meta-analysis because they were all relatively small, included different classes of interventions, and had differing subpopulations. Because of the varying outcomes and uncertainty of this intervention, the panel chose not to make any recommendations at this time.

Antiplatelet Agents: One randomized controlled trial was identified that addressed the use of aspirin and simvastatin in patients with PAH receiving background therapy.[36] No difference was found in the primary outcome, 6MWD, between the aspirin and placebo group (−0.5 m; 95% CI, −28.4 to 27.4 m). There is currently insufficient evidence to recommend for or against the use of antiplatelet therapy for PAH.

TABLE 7] International Society for Heart and Lung Transplantation Recommendations: Referral for Transplantation for PAH

WHO FC III (with worsening symptoms despite optimal therapy)
WHO FC IV symptoms
Rapidly progressive disease
Use of parenteral PAH therapy regardless of symptoms or FC
Known or suspected pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis

FC = functional class; WHO = World Health Organization. See Table 1 legend for expansion of other abbreviation.

SSRIs: One retrospective cohort study was identified that assessed SSRI use in patients with PAH.[35] Kawut et al[35] found that use of SSRIs did not significantly improve survival outcomes (HR, 0.53; 95% CI, 0.07-3.9; $P = .53$). At this time, there is insufficient evidence to recommend for or against the use of SSRIs in patients with PAH.

Additional Considerations

Despite the progress in medical therapy for PAH, there are still a significant number of patients who do not adequately respond to—or who are unable to tolerate—maximal medical therapy. For these patients, lung or heart-lung transplantation continues to be an important therapeutic option that provides substantial improvements in long-term survival and quality of life.

Current guidelines from the International Society for Heart and Lung Transplantation recommend early counseling about transplant and early referral to a transplant program to minimize risks of delay of timely listing for transplantation for potential candidates (Table 7).

Bilateral lung transplant is the most common transplant procedure for patients with PAH; however, heart-lung transplantation may be required for patients with complex congenital disease and other considerations.

Conclusions

Basic discovery, translational science, and clinical trials continue to advance the treatment of patients with PAH. This document provides an evidence-based update addressing important developments in the utilization of combination therapy, and consensus-based suggestions on the integration of palliative care and exercise training (cardiopulmonary rehabilitation) into overall disease management. A treatment algorithm has been added to

assist the care provider in navigating the guidelines. Dissemination and implementation efforts will follow. Importantly, we continue to suggest early referral to expert centers and collaborative care using sound clinical judgment.

Looking to the future, we strongly encourage the translation of basic discovery into safe and effective new therapies, through the conduct of well-designed clinical trials.

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