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REVIEW

Topic-Based, Recent Literature Review on Pulmonary Hypertension

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Abstract

Pulmonary hypertension is a complex condition but a relatively common manifestation of severe cardiopulmonary disease. By contrast, pulmonary arterial hypertension is uncommon and is more prevalent in young women. To better categorize patients and to guide clinical decision-making, 5 diagnostic groups and associated subgroups characterize the spectrum of disease. A multidisciplinary approach to evaluation and treatment is recommended by published guidelines and often entails referral to a designated pulmonary hypertension center. Several key publications during the last couple of years merit review. The PubMed database was searched for English-language studies and guidelines relating to pulmonary hypertension. The following terms were searched, alone and in combination: *pulmonary hypertension*, *pulmonary arterial hypertension*, *portopulmonary hypertension*, and *chronic thromboembolic pulmonary hypertension*. The focus was on those publications with new information on evaluation and management of pulmonary hypertension between January 1, 2019, and January 31, 2021. Of the subgroups, 2 were of particular interest for this review: portopulmonary hypertension and chronic thromboembolic pulmonary hypertension. Last, available data on the impact of the coronavirus disease 2019 pandemic and newer treatment agents in early trials were selectively reviewed. The review is therefore intended to serve as a practical, focused review of important topics germane to those clinicians caring for patients with pulmonary hypertension.pulmonary hypertension, pulmonary arterial hypertension, right ventricular failure

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Pulmonary vascular disease represents a complex challenge for investigators and clinicians alike. Review of recent literature can be challenging with exponential growth in medical literature. A topic-based, focused review of the last couple of years is likely to be a routine practice for most who wish to remain apprised of relevant additions to clinical knowledge. It is with that intent that we have conducted this focused review of selected topics and associated publications or active research, ranging from pathobiology to future studies of interventional agents, for pulmonary arterial hypertension (PAH).

PATHOBIOLOGY

The pathobiology of PAH remains an area of active inquiry.[1] Two distinct areas of focus are potential treatment targets and genetic or heritable predisposition to PAH. There has not been a new US Food and Drug Administration–approved medication specifically for PAH since 2015; therefore, investigations of new treatment targets remain ongoing. One area of focus is the bridge between vasoconstriction and vascular remodeling.[2,3] Medications that vasodilate may also inhibit pulmonary vascular remodeling; therefore, an understanding of the basic mechanisms potentially identifies additional treatment targets. As such, He et al[3] examined pulmonary arteries from both patients and animals, thereby linking the action of prostanoids on D prostanoid receptor subtype 1 and the induction of mammalian target of rapamycin (mTOR) complex 1. Activation of mTOR complex 1 downregulated D prostanoid receptor subtype 1, thus inhibiting the effectiveness of treprostinil. Of note, mTOR is a fundamental regulator of cellular homeostasis. The study raised the possibility that mTOR inhibition (eg, with rapamycin) in combination with currently

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ARTICLE HIGHLIGHTS

- Pulmonary hypertension often represents a diagnostic and therapeutic challenge.
- Genetic and registry studies have provided additional insight into the demographic and different diagnostic classifications.
- Guideline recommendations substantiate dual oral therapy in low- to intermediate-risk patients but infusion prostanoid therapy in high-risk patients with right-sided heart failure.
- Prognostic scoring tools have emerged to guide assessment in patients with pulmonary arterial hypertension.
- Referral to pulmonary hypertension centers often facilitates the complex evaluation and treatment while offering opportunities to study new treatment modalities.

available prostanoid therapy may be an effective treatment strategy.[3]

Important work continues to identify new mutations predisposing or contributing to PAH. Rhodes et al[4] used data from 4 international case-control studies of 11,744 individuals with genome-wide association studies to identify new associations, such as *SOX17* that alters gene regulation through an enhancer in endothelial cells. In addition, the HLA-DPA1/DPB1 genotype was strongly associated with worse survival.[4] Interestingly, analysis from the United States Pulmonary Hypertension Scientific Registry (USPHSR) revealed that genetic testing reclassified 18% of idiopathic PAH (IPAH) diagnoses and 5% of associated PAH (APAH) diagnoses as heritable PAH.[5] Whereas advances in genetic testing and genomics are encouraging, the only strict guideline for screening is that genetic counseling be provided to address complex issues such as incomplete penetrance, psychosocial burden, reproductive decisions, and genetic discrimination (eg, by employers or insurers).[6] Consideration for referral to a genetic counselor is reasonable in patients with IPAH, particularly if there is a family history of PAH.

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Pulmonary hypertension (PH) is classified into 5 diagnostic groups (Table 1).[7] The USPHSR contributed additional data to the understanding of the current PAH demographic.[5] From 2015 to 2018, of 979 potentially eligible patients, 499 were analyzed. The average age was 56 years, and 79% were women. In the distribution of subgroups with group 1 PAH, half were either IPAH or heritable PAH and half were APAH. Whereas the general demographic and clinical characteristics were similar to the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL; Table 2),[5,8] the time from symptom onset to diagnosis by right-sided heart catheterization remained problematic (1.9 vs 2.8 years). Fortunately, more patients (66% vs 54%) were treated with combination therapy, considering the results of the AMBITION trial.[9,10] Nonetheless, one-third of the USPHSR patients were receiving monotherapy, potentially representing an opportunity for more aggressive treatment.[5]

DIAGNOSTICS

There were important revisions to the PAH definition and diagnostic classification by the 6th World Symposium on Pulmonary Hypertension (WSPH). Notably, the diagnostic threshold for mean pulmonary artery pressure was lowered to greater than 20 mm Hg.[7] The 6th WSPH revised definition for diagnosis did not imply treatment of patients in the range of 21 to 24 mm Hg but rather close monitoring.[7] Whereas the intent was to provide an opportunity for earlier detection, particularly in certain risk groups such as scleroderma, the disparity between the diagnostic and treatment definitions may create confusion for providers and patients.[11,12] The 6th WSPH also revised the diagnostic classification scheme (eg, adding specific categories for long-term responders to calcium channel blockers).[7] The changes from the 5th WSPH are summarized in Table 1 but will not have an impact on most patients with PAH.

The importance of understanding the hemodynamic basis of PH and PAH as diagnosed by right-sided heart catheterization was reinforced in 2 recent reviews.[13,14] Appreciation of the pathophysiology and

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TABLE 1. Diagnostic Classification From the 6th World Symposium on Pulmonary Hypertension

Group	Subgroups	Change from 5th WSPH	Comment
1 PAH	1.1 IPAH 1.2 HPAH 1.3 Drug and toxin induced 1.4 Associated PAH 1.4.1 CTD-PAH 1.4.2 HIV-PAH 1.4.3 POPH 1.4.4 CHD-PAH 1.4.5 Schistosomiasis 1.5 PAH long-term responder to CCB 1.6 PAH with PVOD/PCH 1.7 Persistent PH of newborn	Added 1.5 for long-term responders to CCB Changed 1′ to 1.6 for PVOD/PCH Changed 1″ to 1.7 for PH of newborn	1.1 IPAH and 1.4.1 CTD-PAH are most common 1.2 Advances in genetic testing are noteworthy 1.5 Uncommon, but a distinct subgroup 1.6 PVOD/PCH is rare, but a subgroup is EIF2AK4^{+}
2 PH due to left heart disease	2.1 HFpEF 2.2 HFrEF 2.3 Valvular heart disease 2.4 CHD with postcapillary PH	More specific wording for 2.4 to clarify congenital or acquired cardiovascular conditions that produce postcapillary PH	Group 2 PH is the most common cause of PH
3 PH due to lung diseases or hypoxia	3.1 OLD 3.2 RVD 3.3 Mixed OLD and RVD 3.4 Hypoxia without lung disease 3.5 Developmental lung disorders	Consolidated PH due to sleep disorders, hypoventilation, and high altitude to 3.4 hypoxia without lung disease	Group 3 subgroups reduced from 7 to 5
4 PH due to PA obstructions	4.1 CTEPH 4.2 Other PA obstruction	Established new subcategories 4.1 for CTEPH and 4.2 for other PA obstruction	Tumor obstruction formerly in group 5.4
5 PH with unclear or multifactorial mechanisms	5.1 Hematologic disorders 5.2 Systemic and metabolic disorders 5.3 Others 5.4 Complex CHD	Consolidated old 5.2 systemic and 5.3 metabolic into new 5.2 systemic and metabolic disorders 5.3 is now others 5.4 is now complex CHD	5.2 includes sarcoidosis PH 5.3 includes fibrosing mediastinitis

CCB, calcium channel blocker; CHD, congenital heart disease; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; EIF2AK4, eukaryotic translation initiation factor 2α kinase 4; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HIV, human immunodeficiency virus; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; OLD, obstructive lung disease; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; POPH, portopulmonary hypertension; PVOD, pulmonary veno-occlusive disease; RVD, restrictive lung disease; WSPH, World Symposium on Pulmonary Hypertension.

Data from *Eur Respir J*.[7]

TABLE 2. Demographic and Clinical Characteristics From REVEAL Compared With the USPHSR[a,b]

Characteristic	REVEAL (2006-2007)[8]	USPHSR (2015-2018)[5]
No. of patients	2525	499
Age (y)	53.0 (14.0)	55.8 (15.0)
Sex, female	2007 (79.5)	392 (78.6)
NYHA FC III[c]	1153 (50.0)	225 (45.2)
IPAH	1167 (46.2)	218 (43.6)[d]
APAH	1280 (50.7)	256 (51.3)[d]
Time to diagnosis (y), median	1.1	0.8
Time to diagnosis (y)	2.8 (0.1)[e]	1.9 (3.5)
Mean pulmonary artery pressure (mm Hg)	50.7 (13.6)	49.4 (13.2)
Pulmonary wedge pressure (mm Hg)	9.1 (3.5)	10.2 (4.2)
Cardiac index (mL/min/m^2)	2.4 (0.8)[f]	2.4 (0.8)[f]
Combination therapy	1008 (41.3)[g]	323 (65.8)[h]

[a]APAH, associated pulmonary arterial hypertension; FC, functional class; IPAH, idiopathic pulmonary arterial hypertension; NYHA, New York Heart Association; REVEAL, Registry to Evaluate Early and Long-term PAH Disease Management; USPHSR, United States Pulmonary Hypertension Scientific Registry.

[b]Categorical variables are presented as number (percentage). Continuous variables are presented as mean (standard deviation) unless otherwise noted.

[c]Study used n=498 for NYHA FC.

[d]Diagnostic classification before genetic testing (see text).

[e]REVEAL study used standard error rather than standard deviation.

[f]Cardiac index by either thermodilution or Fick method from REVEAL and by Fick from USPHSR data. Of note, REVEAL reported pulmonary vascular resistance index and USPHSR reported pulmonary vascular resistance; therefore, pulmonary vascular resistance was not included in the table.

[g]Study used n=2438 for treatment data.

[h]Study used n=491 for treatment data.

proper procedural technique cannot be overemphasized.

Overall, the diagnostic algorithm for evaluation of PH has not changed substantially between guidelines published in 2015 and the 6th WSPH, except for a greater emphasis on early referral to a PH center for evaluation and complex treatment.[15,16] The goal of the clinician is to confirm PH by right-sided heart catheterization if screening echocardiography demonstrates elevated right-sided heart pressures with either right ventricular (RV) dilation or RV systolic hypokinesis. Clinicians should exclude or confirm chronic thromboembolic disease with nuclear medicine ventilation-perfusion scan, which is preferred to chest computed tomography angiography.[17] Further evaluation for diagnostic subgroup and disease status is required to determine best treatment recommendation. Referral to a PH center is generally advisable.

Exercise-induced PH remains a controversial area because of variances in exercise stress protocols, definition, and lack of approved PAH therapies for that indication. Nonetheless, there was a nice review of exercise hemodynamics specific to the assessment and diagnosis of exercise-induced PH.[18] The review included the differentiation of normal exercise physiology (pulmonary artery pressure/cardiac output slope of >3 mm Hg/L per minute) and that associated with elevated pulmonary vascular resistance (PVR), with an emphasis on upright position for exercise.[18] Although there is no specific indication for treatment with approved PAH medications, an elevated pulmonary artery pressure/cardiac output slope portends worse outcome.[19]

TREATMENT

Qualitative and quantitative risk assessments have categorized patients into low, intermediate, and high risk to guide treatment decisions (Table 3).[9,16,20] Indeed, risk assessment indicates appropriate PAH medications and

TABLE 3. Treatment Guidelines Based on Diagnostic Group and Risk Assessment[a]

Diagnostic group	Treatment guideline
Group 1 PAH	Choose treatment on the basis of risk assessment. For low to intermediate risk Vasoreactive[b]: trial calcium channel blocker therapy with close follow-up to ensure long-term response Nonvasoreactive: combination oral therapy with an ERA plus a PDE5 inhibitor For high risk Infusion prostanoid therapy with either treprostinil or epoprostenol (strongest recommendation) in combination with oral therapy
Group 2 PVH	Address underlying cardiac condition. Avoid PAH-specific medications unless in clinical protocol or study.
Group 3 PH	Address underlying pulmonary condition. If ILD-PH, consider inhaled treprostinil with regular reassessments to determine response. Otherwise, avoid PAH-specific medications unless in clinical protocol or study.
Group 4 CTEPH	Refer to PH center for evaluation for potential pulmonary thromboendarterectomy. Whereas riociguat has an FDA-approved indication for inoperable CTEPH, the determination of inoperability should be made by the PH center. In addition, eligibility for balloon pulmonary angioplasty requires expert center review.
Group 5 PH	Address underlying associated condition. Avoid PAH-specific medications unless in clinical protocol or study.

[a]CTEPH, chronic thromboembolic pulmonary hypertension; ERA, endothelin receptor antagonist; FDA, US Food and Drug Administration; ILD-PH, interstitial lung disease–associated pulmonary hypertension; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5; PH, pulmonary hypertension; PVH, pulmonary venous hypertension.

[b]Decrease in mean pulmonary artery pressure by at least 10 mm Hg to less than 40 mm Hg while maintaining or increasing cardiac output in response to an acute vasodilator such as inhaled nitric oxide.

Data from *Eur Heart J*[16] and *Eur Respir J*.[7]

whether combinations are beneficial. To that end, several important treatment trials merit mention. Reinforcing the AMBITION trial results,[9,10] Sitbon et al[21] demonstrated the benefit of initial treatment with macitentan plus tadalafil. Of note, it was an open-label observation study of 46 patients during 16 weeks with reduction in mean (standard deviation) PVR from 11.7 (4.7) to 6.5 (3.6) Wood units ($P<.0001$). Improvements were also seen in New York Heart Association (NYHA) functional class, N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels, and 6-minute walk distance (6MWD). Whereas the trial design warrants caution, the favorable combination of an endothelin receptor antagonist (ERA) and phosphodiesterase type 5 (PDE5) inhibitor has substantial supporting evidence.[21] Indeed, upfront combination therapy with ambrisentan and tadalafil compared with monotherapy demonstrated a reduction in hospitalizations.[10]

Conversely, the TRITON trial was a multicenter, randomized, double-blind, placebo-controlled trial (MCRDBPCT) of 247 patients comparing upfront therapy with macitentan, tadalafil, and selexipag vs macitentan, tadalafil, and placebo.[22] The primary end point was PVR at week 26. The baseline PVR was approximately 12 Wood units in both groups and approximately 6 Wood units at follow-up assessment, neither clinically nor statistically different. In addition, there was no significant difference in NYHA functional class, NT-proBNP level, or 6MWD. Despite the negative nature of the study, it reinforces the benefit of upfront combination dual therapy with an ERA and PDE5 inhibitor. Interestingly, there was a 41% reduction in the risk of disease progression in the triple-therapy arm (hazard ratio [HR], 0.59; 95% CI, 0.32 to 1.09; $P=.087$); however, the result was not statistically significant.[22] Understanding of the significance of this finding awaits further exploration. It appears challenging to identify a priori which treatment-naïve patients who are not in need of parenteral therapy are going to benefit from triple therapy. Upfront dual therapy for low- to intermediate-risk patients

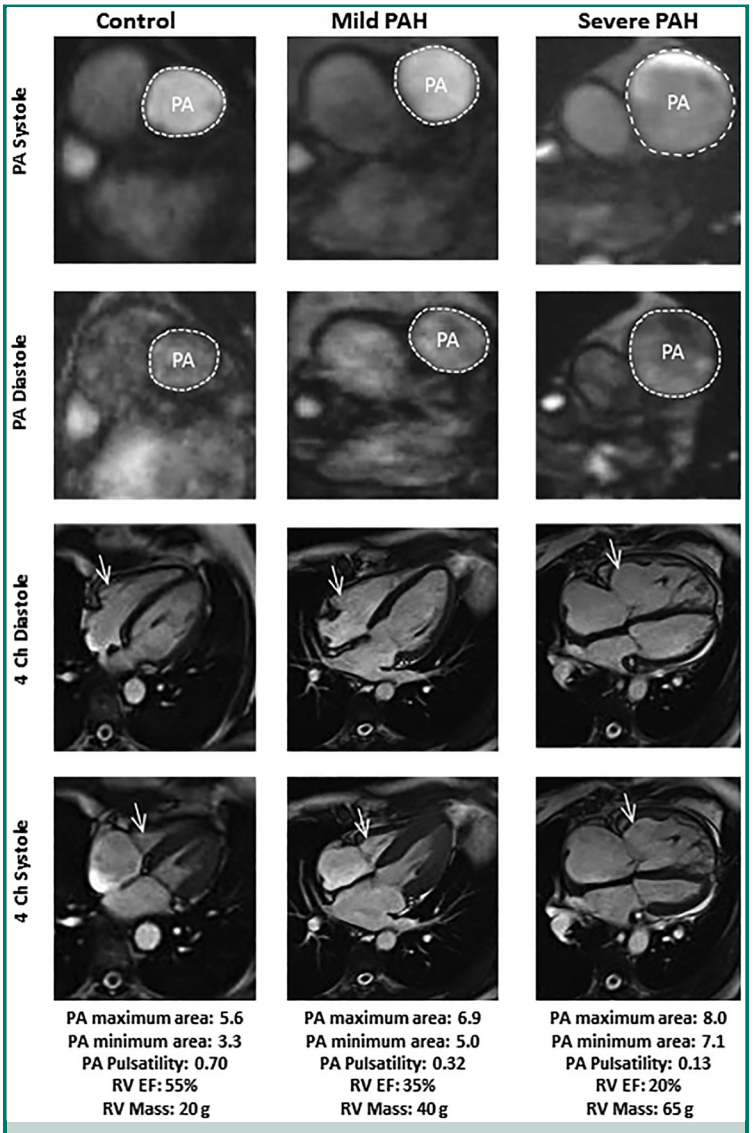

FIGURE. Pulmonary artery pulsatility. Cardiac magnetic resonance images of the main pulmonary artery (PA) and right ventricle (arrow) in representative study participants without compared to those with mild and severe pulmonary arterial hypertension (PAH). Images during cardiac systole and diastole were used to calculate PA pulsatility. Ch, chamber; EF, ejection fraction; RV, right ventricular. (Reprinted by permission from Springer Nature, *International Journal of Cardiovascular Imaging*. Ray JC, Burger C, Mergo P, et al. Pulmonary arterial stiffness assessed by cardiovascular magnetic resonance imaging is a predictor of mild pulmonary arterial hypertension. ©2019.)

(Figure) followed by careful reassessment at 3 months is a reasonable approach based on current data.

More data are now available in support of oral prostanoid therapy with publication of the positive results from the FREEDOM-EV trial.[23] This MCRDBPCT of 690 patients demonstrated an improvement with oral treprostinil added to background oral monotherapy of an ERA or either riociguat or PDE5 inhibitor. Clinical worsening occurred in 346 patients (26%) receiving oral treprostinil compared with 344 (36%) receiving placebo (HR, 0.74; 95% CI, 0.56 to 0.97; P=.0275). The clinical worsening end point was primarily driven by differences in disease progression. There were also reported improvements in NYHA functional class and NT-proBNP level. The median dose of oral treprostinil was 5.5 mg 3 times daily, emphasizing the importance of a commitment to up-titrating to an appropriate dose.[23] In addition, a consensus survey of oral prostacyclin therapy was published this past year.[24] Unfortunately, the survey predated FREEDOM-EV; therefore, it was heavily weighted in favor of selexipag. There were 14 expert consensus statements in the document specific to recommendations to add selexipag for patients receiving dual oral therapy with an ERA and a PDE5 inhibitor. Certain conditions drove the recommendation to escalate therapy and included NYHA functional class II or greater plus intermediate-risk hemodynamics, hospitalization in the last 6 months, and moderate to severe RV dysfunction in patients with "IPAH+" (ie, IPAH, heritable PAH, drug/toxin APAH, and repaired congenital heart disease APAH). In patients with connective tissue disease–associated PAH, any abnormality in RV function, elevation in BNP or NT-proBNP level, or 6MWD less than 440 m led to a recommendation to add selexipag. Most important, infusion prostanoid was strongly recommended for patients with PAH with high-risk hemodynamics despite dual oral therapy.[24]

Because there are only 3 treatment target pathways (ie, prostacyclin, endothelin, and nitric oxide) for the 13 US Food and Drug Administration–approved PAH medications, an improved understanding of whether specific advantages exist for 1 agent compared with another within a treatment target class is needed. For example, PDE5 inhibitors and riociguat, a soluble guanylate cyclase stimulator, both work in the nitric oxide pathway. To that end, the results of the phase

4 REPLACE (Riociguat rEplacing PDE-5i Therapy evaLuated Against Continued PDE-5i thErapy) trial, presented at the 2020 European Respiratory Society by Hoeper et al,[25] add to the available knowledge. The basis of the study involved the conversion from a PDE5 inhibitor to riociguat or continuation of a PDE5 inhibitor in an open-label, randomized fashion with follow-up assessments at 24 weeks. Patients were required to be assigned to NYHA functional class III, with a 6MWD of 165 to 440 m, and could be receiving monotherapy with a PDE5 inhibitor or combined therapy with an ERA. Overall, 226 patients (111 converted to riociguat compared with 115 with continued PDE5 inhibitor) were enrolled. The primary composite end point was clinical improvement in at least 2 of 3 measures: NYHA functional class I or II, improvement in 6MWD, or improvement in NT-proBNP level. Notably, 41% in the riociguat arm met the primary end point compared with 20% continuing PDE5 inhibitor without change (odds ratio, 2.78; 95% CI, 1.53 to 5.06; P=.0007).[25] The study builds on the results of the phase 3 RESPITE study,[26] indicating that conversion from PDE5 inhibition to riociguat may be reasonable in select patients who have persistent NYHA functional class III symptoms and 6MWD less than 440 m.

There is also continued interest in whether the currently approved PAH medications have efficacy in PH groups other than group 1. Riociguat has an approved indication for group 4 chronic thromboembolic PH (CTEPH), but otherwise, guideline recommendations restrict use to group 1 PAH.[16,27] As group 2 and group 3 PH constitute the largest percentage of patients with PH, studies have proliferated in those groups but largely with disappointing results. Indeed, some have been discontinued early because of adverse effects. It is therefore exciting to have the results of the INCREASE trial, which have demonstrated the benefit of inhaled treprostinil in patients with interstitial lung disease (ILD).[28] The study was a MCRDBPCT of 326 patients comparing inhaled treprostinil with placebo in patients with stable ILD or combined pulmonary fibrosis emphysema. The primary end point reached statistically significant difference with an improvement in 6MWD of 21 m at 16 weeks in the treatment group. There was a 39% reduction in time to first clinical worsening event and an improvement in NT-proBNP levels. Interestingly, there was also a 34% reduction in risk for exacerbation of ILD. Although the results are encouraging, quality of life remained unchanged.[28] Regardless, inhaled treprostinil received US Food and Drug Administration approval for group 3 ILD-related PH on April 1, 2021. Treatment of patients with group 3 ILD-associated PH remains challenging, and real-world data should be collected for analysis.[29,30]

OUTCOMES

Several publications have addressed PAH outcomes or burden of disease and associated treatment. Continued efforts to refine measures of disease severity and prognosis have yielded positive results. The improved risk score calculator REVEAL 2.0 incorporates information about hospitalization within the preceding 6 months and estimated glomerular filtration rate among other refinements.[20] Of note, REVEAL 2.0 performed significantly better than the European registry risk scores and categorizations, the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension and the French Pulmonary Hypertension Registry. An abbreviated version that includes only 6 noninvasive variables (REVEAL Lite 2) offers a streamlined option that can be used for longitudinal risk assessment, whereas the full REVEAL 2.0 is preferable for baseline assessment.[20,31] Use of longitudinal risk assessment to make optimal treatment decisions is an important aspect of PAH management.

Regardless of cause, PH has been associated with poor prognosis. Maron et al[32] established an important threshold for PVR in this regard. They performed a retrospective review of patients having undergone right-sided heart catheterization in a US Veterans Affairs health care system cohort with 1-year follow-up. All-cause mortality was increased (HR, 1.17; 95% CI, 1.59 to 1.84;

TABLE 4. New Agents Under Study for Pulmonary Arterial Hypertension

Agent	Target	Route	Early results	Ongoing study
Rodatristat	5-HT hydroxylase	Oral, twice daily	Safety and tolerability	Phase 2b, ELEVATE-2[55]
Seralutinib	PDGFR	Inhaled, twice daily	Safety and tolerability	Phase 2, GB002 2101[56]
Sotatercept	BMPR-II	Subcutaneous injection every 3 weeks	Improvements in NYHA FC, NT-proBNP level, 6MWD, PVR	Phase 3, STELLAR[57]
LIQ861	Prostaglandin	Inhaled, 4 times daily	Improvements in NYHA FC, 6MWD, QOL	OLE[58]

BMPR-II, bone morphogenetic protein receptor 2; FC, functional class; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal pro—B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; PDGFR, platelet-derived growth factor receptor αβ; PVR, pulmonary vascular resistance; QOL, quality of life; 5-HT, tryptophan hydroxylase.

$P<.0001$) in those patients with a PVR of 2.2 Wood units or more. Risk for heart failure hospitalization was also increased (HR, 1.27; 95% CI, 1.13 to 1.43; $P=.0001$).[32] Linking outcome to PVR and RV afterload is logical as patients with PAH who fare poorly have refractory RV failure.[33] Indeed, a retrospective review of 181 patients with PAH treated with dual oral therapy (predominantly ambrisentan plus tadalafil) examined the relationship to PVR in the poor responders (more than a third of the cohort).[34] Suboptimal reductions in PVR were associated with age older than 60 years, male sex, baseline mean pulmonary artery pressure greater than 48 mm Hg with low cardiac index, and elevated right ventricle/left ventricle ratio (<1) with low tricuspid annular plane systolic excursion (<18 mm) by echocardiography. A PVR score was generated on the basis of age, sex, mean pulmonary artery pressure with cardiac index, and right ventricle/left ventricle ratio with tricuspid annular plane systolic excursion to identify those patients likely to be poor responders to dual oral therapy,[34] the implications of which may warrant earlier consideration of infusion prostanoid in light of the negative results from TRITON.[22]

Advanced imaging may also provide markers of more severe disease and potential poor response to therapy.[35] Cardiac magnetic resonance imaging may be useful in this regard for earlier detection and therefore an opportunity for treatment stratification. Pulmonary arterial pulsatility is a surrogate that has been used to assess the presence and severity of PAH. It is calculated as a percentage change in pulmonary artery diameter with RV contraction.[36] Ray et al[37] demonstrated that patients with mild PH had markedly reduced pulmonary arterial pulsatility compared with normal controls (22% vs 53%; $P<.001$) by cardiac magnetic resonance, despite no difference in RV morphology or function (Figure). Pulmonary arterial pulsatility less than 40% resulted in a sensitivity of 95.0% and specificity of 94.4% for detection of PAH.[37] It is conceivable that novel imaging measurements of pulmonary vascular remodeling may serve as reliable end points to assess disease severity and potentially to guide therapeutic decision-making.

Activity levels in patients with PAH have been proposed as a surrogate marker of functional capacity; however, few data are available to support that contention. The concept was specifically addressed in the TRACE study, a multicenter prospective study of 53 patients randomized to either selexipag or placebo for 24 weeks.[38] Activity, characterized as daily life physical activity, was no different in the 2 groups. Of note, the cohort was a predominantly low-risk group on stable dual background therapy, and patients were not actively encouraged to increase activity during the study.[38] Although activity levels remain popular with the proliferation of wearables, more data are needed to understand their role in PAH outcome studies.

It may be difficult to completely appreciate the psychosocial impact of PAH and the burden associated with complex and expensive medical therapy. Descriptive results of survey data in a single-center cohort and a more diverse group who volunteered at the Pulmonary Hypertension Association international conference provide some additional insight.[39] Notably, patients reported considerable physical and psychological burden with PAH and its related treatment, with remarkable financial challenges as well.[39]

Not surprisingly, hospitalization for PAH is associated with poor outcome.[20,40] For patients with recurrent hospitalization for right-sided heart failure due to PAH refractory to maximal medical therapy, palliative care may be the most appropriate option. Unfortunately, palliative care services appear underused in hospitalized patients with PAH.[41]

SPECIAL POPULATIONS AND TOPICS

Advances in the assessment and management of 2 PH subgroups, CTEPH and portopulmonary hypertension (POPH), warrant mention. The initial results of the US CTEPH Registry were presented at the American Thoracic Society international meeting.[42] The comparison included those patients who underwent pulmonary thromboendarterectomy (PTE) and those managed without PTE in registry data collected from 30 US centers, approximately 750 patients. Predictably, patients with CTEPH who underwent PTE demonstrated improved symptom and functional status with better hemodynamics and less need for ongoing PAH therapy. Notably, in a subgroup analysis, those patients considered ineligible for PTE were predominantly of Black race, advanced age, higher body mass index, and increased PAH-specific treatment.

New data in support of medical therapy for inoperable patients were provided in the MERIT-2 trial.[43] The MERIT-1 trial was a 24-week MCRDBPCT that demonstrated the benefit of macitentan in a cohort of 80 patients with CTEPH ineligible for surgery.[44] MERIT-2 assessed the long-term safety, tolerability, and efficacy of macitentan in 76 of the original 80 patients. Favorable gains in NYHA functional class and 6MWD were generally maintained at 6 months. Overall, those patients originally in the macitentan arm of MERIT-1 did better.[43]

An emerging option for inoperable or residual CTEPH is balloon pulmonary angioplasty (BPA).[45,46] The RACE trial compared BPA with riociguat, demonstrating a larger improvement in PVR at 26 weeks with BPA (geometric mean reduction: 60% in BPA arm, 32% in riociguat arm; $P<.0001$) but with more adverse effects (serious adverse events: 50% in BPA arm, 26% in riociguat arm).[46] Mayo Clinic experience with BPA was reviewed in 31 patients with inoperable CTEPH or residual CTEPH after surgical PTE.[45] As a viable alternative, BPA offered acceptable risks and improvement in NYHA functional class, exercise tolerance, ventilatory efficiency with improved ventilation/perfusion mismatch, and hemodynamics.[45]

Portopulmonary hypertension is a subgroup of group 1 PAH (group 1.4.3) but is often absent in PAH drug trials to avoid issues of excessive reports of hepatotoxicity, among other reasons. The ERA class has had this potential as bosentan has confirmed risk of elevated transaminases in approximately 10% of patients with group 1 PAH without previous liver disease.[47] Fortunately, later generation ERAs, ambrisentan and macitentan, have not had liver toxicity compared with placebo.[48] Nonetheless, there has been reasonable caution for use of the later generation ERAs in patients with known end-stage liver disease and PH (ie, POPH). Macitentan has shown efficacy (35% reduction in PVR) and safety in the PORTICO trial,[49] and more recently, a multicenter, prospective, open-label study of ambrisentan in 31 patients also demonstrated tolerability.[50]

Ultimately, patients with POPH may undergo liver transplant (LT) if the PAH can be adequately controlled with treatment. Clinical outcomes for patients with POPH were examined in pooled data from all 3 Mayo Clinic LT centers.[51] Of 228 patients with POPH, 50 underwent LT. Significant hemodynamic improvement was observed after PAH-targeted therapy, and after LT, 21

(42%) patients were able to discontinue and to remain off PAH-targeted therapy. The 1-, 3-, and 5-year unadjusted survival rates after LT were 72%, 63%, and 60%, respectively. An elevated PVR before LT was associated with worse survival rate (HR, 1.91), again emphasizing the importance of RV afterload on outcome.[51]

By comparison, retrospective review of a large (637 patients) French cohort demonstrated 1-, 3-, and 5-year survival rates after LT of 84%, 69%, and 51%, respectively.[52] Most patients (90%) received PAH-specific therapy with improved NYHA functional class, 6MWD, and PVR. A subgroup of 117 patients had POPH diagnosed while undergoing pre-LT evaluation, 63 (54%) of whom subsequently underwent LT. Almost all (60/63 [95%]) received PAH-specific therapy, 24% of whom were bridged with intravenous administration of epoprostenol. Survival in the subgroup receiving LT was significantly better, with 1-, 3-, and 5-year survival rates of 92%, 83%, and 81%, respectively, more favorable than the Mayo Clinic series.[51,52] A single-center experience of 24 POPH patients with excellent outcomes was published by the University of Wisconsin group.[53] All patients were optimized on medical therapy with 1-, 3-, and 5-year survival rates of 96%, 91%, and 91% in the cohort that underwent transplant. Of those receiving parenteral PAH therapy, all were weaned during a median time of 7 months. Overall, 62% of patients had all PAH therapy discontinued after LT. Despite advances in medical therapy, long-term survival for patients with POPH remains modest; however, combined with LT, it may result in improved outcome.

The COVID-19 pandemic has reshaped health care in many ways. There is the immediate concern among providers for the impact on their patients with underlying cardiopulmonary morbidity. To gauge the risk to patients with PAH, Lee et al[54] surveyed PH centers accredited by the Pulmonary Hypertension Association participating in the Pulmonary Hypertension Association Registry. Most of the centers (75%) indicated that the case rate in patients with group 1 PAH and group 4 CTEPH (both groups are included in the Pulmonary Hypertension Association Registry) was like that of the general population. Far more concerning was a reported hospitalization (30%) and mortality (12%) rate that appeared worse than in the general population. In addition, significant shifts in health care delivery included limited access to diagnostic testing and use of telehealth.

NEW TARGETED TREATMENTS

Efforts to identify new targets for PAH therapy and related effective agents are of considerable interest. A few examples with ongoing activity are listed in Table 4.[55-57] Sotatercept (Acceleron Pharma, Inc), in a phase 2 study (PULSAR) of 106 patients, demonstrated a 34% reduction in PVR compared with placebo in both the 0.3 mg/kg and 0.7 mg/kg doses administered subcutaneously every 3 weeks.[59] Improvements were also seen in NYHA functional class, NT-proBNP level, and 6MWD.[59] A phase 3 trial (STELLAR) comparing sotatercept with placebo in patients with group 1 PAH on background therapy is ongoing.[57] Rodatristat ethyl (Altavant Sciences, Inc), designed to block peripheral serotonin production, will be studied in a phase 2b MCRDBPCT with 3 arms, 300 mg twice daily, 600 mg twice daily, and placebo twice daily, with the primary end point of PVR at 24 weeks.[55] Seralutinib (Gossamer BIO), an inhaled dry powder tyrosine kinase inhibitor that targets platelet-derived growth factor receptor αβ, colony-stimulating factor 1 receptor, and cKit, has completed a phase 1b trial. A phase 2 trial examining the effect on PVR at 24 weeks is ongoing.[56]

There are also multiple studies in progress to establish the safety and efficacy of dry powder formulations of inhaled treprostinil.[58,60,61] For example, data from the phase 3 INSPIRE trial for Liquidia Technologies' dry powder formulation of inhaled treprostinil (LIQ861) demonstrated safety, tolerability, and modest improvement in NYHA functional class, 6MWD (median 10 m), and quality of life.[62]

Unfortunately, not all patients respond to approved PAH-specific therapy or benefit from a clinical trial; therefore, lung transplant may be the only viable treatment option. Progressive RV failure may also occur precipitously, so recommendations from the 6th WSPH provide useful guidance for bridging to transplant.[63] A detailed therapeutic approach ranging from medical management to extracorporeal lung support allows assessment for transplant eligibility. One-year survival after lung transplant for PH is greater than 90% in experienced centers.[63]

CONCLUSION

Pulmonary vascular disease represents a complex challenge for investigators and clinicians alike. Review of recent literature can be challenging with the exponential growth in medical literature. A topic-based, focused review offers a methodology for remaining current without the daunting task of a more comprehensive literature compilation. It is with that intent and focus that we provide this review of the included topics with select citations and areas of inquiry.

Abbreviations and Acronyms: **APAH,** associated pulmonary arterial hypertension; **BPA,** balloon pulmonary angioplasty; **CTEPH,** chronic thromboembolic pulmonary hypertension; **ERA,** endothelin receptor antagonist; **ILD,** interstitial lung disease; **IPAH,** idiopathic pulmonary arterial hypertension; **LT,** liver transplant; **MCRDBPCT,** multicenter, randomized, double-blind, placebo-controlled trial; **mTOR,** mammalian target of rapamycin; **NT-proBNP,** N-terminal pro–B-type natriuretic peptide; **NYHA,** New York Heart Association; **PAH,** pulmonary arterial hypertension; **PDE5,** phosphodiesterase type 5; **PH,** pulmonary hypertension; **POPH,** portopulmonary hypertension; **PTE,** pulmonary thromboendarterectomy; **PVR,** pulmonary vascular resistance; **REVEAL,** Registry to Evaluate Early and Long-term PAH Disease Management; **RV,** right ventricular; **6MWD,** 6-minute walk distance; **USPHSR,** United States Pulmonary Hypertension Scientific Registry; **WSPH,** World Symposium on Pulmonary Hypertension

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