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## UNMET NEEDS AND BURDEN OF DISEASE

### Introduction and Overview

**Dr. Mayeux**: Hello! I am Jennalynn Mayeux. I am a nurse practitioner, and I am honored to join you and PAH expert, Dr. Aaron Waxman, on your journey through the modules in this PAH subway. The title of this presentation is Optimizing Outcomes in Pulmonary Arterial Hypertension: Evidence, Innovation and Individualization. It's really important for us to, of course, look back and where we've been, but also looking forward to what comes next and the innovations in pulmonary hypertension.

### Advances in Pulmonary Hypertension

I have been privileged to be in pulmonary arterial hypertension for a while now and seeing these advances, including new sets of guidelines that expand our thinking and also bring in more evidence-based therapies and diagnoses and help us better tailor treatments to the patients and individualize our care. 2022 brought about our most recent set of guidelines for the diagnosis and treatment of pulmonary hypertension. Most importantly, the definition of pulmonary hypertension was changed just a little bit again, bringing PVR down to greater than 2, in addition to a mean pulmonary pressure of greater than 20 and then also a mean pulmonary or a wedge pressure of 15. 2024 was another exciting year, not only did we have the World Symposium of Pulmonary Hypertension treatment algorithms released for pulmonary hypertension which included sotatercept, which we will talk about today as it is our most novel, newest therapy. The A DUE trial continued to support the progress of advanced, up-front dual combination therapy for our patients with PAH. We were able to look at macitentan and tadalafil in a fixed-dose combination tablet, 1 tablet, once a day compared to macitentan or tadalafil in monotherapy, and there was a benefit in PVR and walk distance for those patients, further supporting what we've been doing and what is within these algorithms and these treatment guidelines.

2025 is an exciting year because we were looking at sotatercept in patients with more severe disease who are at high risk of death compared to the well-treated group in which it was initially studied. And then looking forward to 2026, we are seeing several new agents and even some agents that have been used in other disease processes being reignited for our pulmonary hypertension patients.

### Burden of Disease

As exciting as these advances are, we still recognize there are several unmet needs among our patient population. As with any patients with chronic disease, we know that there is a long struggle before a patient gets a diagnosis. Significant diagnostic delay, leading to potentially more frustration and increased morbidity as patients are declining in functional class as well as having to walk through our healthcare systems in which not everybody has equal access to treatment. Maybe they're not in an area where there is a local care facility or the expertise that is there, as well as the economic burden of having health insurance, paying for copays and the time that it may take to get those diagnoses as well as those tests, and the relationships required to best treat this disease.

## PATHOPHYSIOLOGY OF PAH

**Dr. Waxman**: Pulmonary arterial hypertension is felt to be a progressive disease. This disease is typified by ongoing pulmonary vascular remodeling, and what that means is that the blood vessels of the lung, usually starting out very distal and progressing proximally, have abnormal proliferation of both our endothelial cells and smooth muscle cells, as well as infiltration of inflammatory cells and connective tissue cells that result in some progressive fibrosis. We now know that most of the symptoms, and ultimately the long-term prognosis and morbidity and mortality, are directly related to preservation of right heart function. As that pulmonary vascular remodeling progresses, the right heart adapts to the increased pressure, resistance and reduced compliance by increasing the thickness of the muscle. It hypertrophies. Over time, that progressive adaptation actually shifts into a maladaptive phase where the ventricle starts to dilate, become weaker and starts to fail. Part of that failure is a change in metabolism where it becomes less efficient, something we call the Warburg effect. There's also changes in reactive oxygen species causing damage to cardiomyocytes. There's increased inflammation, increased


cell death and increased fibrosis, ultimately leading to right hear failure and death.

## DIAGNOSIS OF PAH

### Symptoms, Diagnostic Assessment and Referral

**Dr. Mayeux**: Next, we are going to talk about the diagnosis of pulmonary hypertension. Of course, our patients initially start with a symptom that brings them to our office and raises the concern. Most often in pulmonary hypertension or pulmonary arterial hypertension most specifically, patients will report dyspnea, nonspecific dyspnea, sometimes short of breath going to the grocery store, sometimes short of breath going up the stairs. Some patients will present just feeling exhausted with any physical exhaustion or any physical activity. Some will be gaining more water weight and fluid and present pretty edematous. The red flag of red flags for me is syncope. If a patient is losing consciousness, particularly when they're exertional, that tells us that we are in a decompensated state. Rarely, we can sometimes see the symptoms of hemoptysis or maybe hoarseness or dysphonia, but most often we are seeing shortness of breath with our patients who are presenting, particularly early on their course.

When a patient presents with shortness of breath, oftentimes it's to a general practitioner or their primary care provider and of course we do a thorough history and a physical exam. Dyspnea is fairly nonspecific, so it would require additional studies. The recommendation is EKG, NT-proBNP or BNP, which is a blood test, and then oxygen saturations. And with that history, combined with the story of the symptoms, and maybe the other presenting factors, other known risk factors for the patient, we can go down the track either more towards a lung assessment or a heart assessment. Thinking of the causes of dyspnea—which can be cardiac, can be pulmonary—the next step would be to think if we are feeling this is pulmonary, let's get some pulmonary function tests, potentially an arterial blood gas, checking for hypoventilation syndromes or checking for low oxygen levels, a chest x-ray, we see those big pulmonary arteries, maybe even a CT scan looking for other sorts of lung disease, maybe even a cardiopulmonary exercise test. When it comes to thinking that maybe there's a cardiac component, an echocardiogram can speak volumes and give us an idea of the risk of pulmonary hypertension as well as rule out other causes, including left heart disease. We will see cardiac MRIs which can give us further assessment of structures and some function, and also cardiopulmonary exercise testing which overlaps both the cardiac and the pulmonary worlds.

Based on the results of these tests, we're able, as providers, to come up with an assessment of what we think may be happening, and appropriately refer to the centers, particularly in the diagnosis of pulmonary hypertension for right heart catheterization and a comprehensive pulmonary hypertension work-up which would include a ventilation perfusion scan looking for the diagnosis of CTEPH which stands for chronic thromboembolic pulmonary hypertension, in which a VQ scan is the only test that can truly rule it out. Once we get to the right heart catheterization, we can make a couple of different determinations as far as treatment planning. Diagnosis of pulmonary hypertension is a mean pulmonary arterial pressure of greater than 20 mmHg as well as a PVR of greater than 2, and typically a wedge pressure of less than 15 is included in that definition as well.

When a patient goes in for right heart catheterization, we're asking ourselves a few questions. First of all, what is their risk? How severe is their pulmonary hypertension? We first look at do they have pulmonary hypertension, yes or no. Is that average pressure greater or less than 20? If it is greater than 20, we can make that diagnosis of pulmonary hypertension. We will also look at cardiac output, cardiac index and what we call the wedge pressure which is how we assess the left heart and volume assessment. Pulmonary artery wedge pressure, also referred to as pulmonary capillary wedge pressure, is measured to give us an idea if the patient has post-capillary or pre-capillary pulmonary hypertension. Pre-capillary pulmonary hypertension includes pulmonary arterial hypertension, can include pulmonary hypertension secondary to hypoxia or lung disease, and then CTEPH as well as this other mix of pulmonary hypertension groups that we'll go over in another module. Within that right heart catheterization assessment, we can make that diagnosis of pulmonary hypertension or what type of pulmonary hypertension that patient may have.

### World Health Organization Classification

A right heart catheterization tends to be able to give us many answers, but it cannot prove a diagnosis one way or another. We have to use our clinical skills and judgment, as


well as conversations with the patient to recognize and identify the risk factors for each type of pulmonary hypertension or each group. The World Health Organization has a classification of 5 groups of pulmonary hypertension. Group 1 is among the most rare. It is pulmonary arterial hypertension. This is a true vascular disease. It can be idiopathic, meaning that it is not related to anything else. This is the disease that we typically think of affecting women, potentially of child-bearing age, classically PAH presenting with right heart failure. There is a heritable type of pulmonary hypertension. We'll bring genetics and genetic counseling into our patients' visits as well as workups. And then other associated conditions, most commonly autoimmune diseases, particularly systemic sclerosis. We are seeing an increased epidemic of pulmonary hypertension secondary to methamphetamine use. We can see PAH secondary to HIV or liver disease, portal pulmonary hypertension for example, and some other rare conditions as well. Most of the time, pulmonary arterial hypertension is secondary to another underlying disorder, although patients can certainly have idiopathic PAH.

Group 2 pulmonary hypertension is very common. The prevalence of pulmonary hypertension, so just meaning high blood pressure in the lungs, mean pressure greater than 20, is probably about 1% globally. That's a lot of people. Pulmonary arterial hypertension is a much more rare subset, less than 10% of patients will have PAH. The large grouping that's left, that 90-plus percent, will have PH associated with left-sided heart dysfunction or disease or pulmonary hypertension associated with low oxygen levels. And that's really an and/or because many of our patients will have overlapping disease, which takes me into pulmonary hypertension associated with lung disease. That includes obesity, hypoventilation, interstitial lung disease, COPD, any disease that can cause low oxygen levels can contribute to pulmonary hypertension. Group 4 is CTEPH, which stands for chronic thromboembolic pulmonary hypertension, as well as the potential for other pulmonary obstructions. This is where the ventilation perfusion scans are incredibly important because our patients with CTEPH may not have a history of embolic disease, so no DVTs, no history of PEs, and we may get that VQ scan and it can be largely abnormal or, if we see a patient who has a history of a PE and now has pulmonary hypertension, there is a suspicion for CTEPH and it needs to be ruled out with that ventilation perfusion scan. And lastly, group 5 is a smattering of other disorders, particularly hematologic disorders or other systemic disorders. And it's fairly rare, as in the case of sarcoidosis.

### Key Concepts

Our key concepts are that our patients' symptoms, upon presentation, may vary and they're really based on disease severity. Some patients may go from mild shortness of breath all the way to severe volume overload and syncope. And their right heart catheterization is essential for diagnosing the pulmonary hypertension and helping us figure out what is the etiology and how best to treat and maintain that patient.

When we work up our patients, this includes many variables, both heart- and lung-related. We are looking at echocardiograms, we're looking at pulmonary function tests to come up with a complete picture of risk and how best to manage patients. Dr. Waxman, this is a complicated disease process. What do you find to be the most challenging part of working up pulmonary hypertension?

**Dr. Waxman**: I think one of the key things, as you mentioned, is dyspnea, and the vast majority of these patients present with unexplained shortness of breath. And being able to, 1, even think of the disease is critical, but doing a systematic workup to figure out why they're short of breath. And one thing we've learned is that if you do an echo, you do a full pulmonary function, including diffusing capacity, and some sort of chest imaging, it should at least give you information to direct you down a certain path. And I think, importantly, what's stressed here too is the right heart cath is essential. We would never start treatment without a right heart cath. In part, this is a hemodynamic disease. The other components of these concepts really come down to staging the disease, if you will, really providing enough data to be able to tell the patient what they've got, how bad it is, how progressive it might be and how we're going to treat it. And many of these things like the 6-minute walk and cardiopulmonary exercise testing, help really funnel into a prognostication and risk stratification.

**Dr. Mayeux**: I completely agree and I think it's an important time to highlight the importance of expert centers where we can get reliable diagnostics, particularly those right heart catheterizations and exercise assessments.


## GOALS OF TREATMENT

### GUIDELINE-DIRECTED GOALS

**Dr. Waxman**: Once a diagnosis is made, we start to think about how to treat a patient and I like to think of 4 fundamental treatment goals. Not that they're the only goals, but I see these as important. Obviously, we want to improve survival of the patient, and we also want to improve their symptoms and quality of life. If we can improve symptoms, ie, make them less short of breath, then we should also see an improvement in exercise tolerance and exercise capacity. And I think, equally importantly, we want to limit disease progression.

### ROLE OF RISK STRATIFICATION

When we start to think about how we're going to treat a patient, we like to put them into some sort of risk category, and there are a number of risk calculators out there. The one we typically use at the time of diagnosis is a 3-strata model which may be the REVEAL risk calculator or the COMPERA 3-strata model. Both of these have a lot of overlaps, but fundamentally they break a patient's risk categories down into low, intermediate and high risk. They're fairly common sense as far as any patient with heart failure and generally you would get a numeric readout based on what findings the patient has and then, depending on that risk category, we will decide on what treatments we might use and in what combinations.

Once a patient is on treatment, we like to recategorize them and make sure that they're making progress. This is the 4-strata model, based on the COMPERA risk calculator. And what's very nice about this calculator is it breaks it down into 4 different categories which really just are more precise about how that patient is expected to progress and prognosis overall. And this would also guide the next stage of treatment if we need to get more aggressive or we can think about holding tight or even thinking about backing off.

### KEY CONCEPTS

Key concepts in thinking about risk stratification and I want to get Dr. Mayeux back on. Obviously, as I already mentioned, the goal of treatment is to improve morbidity and mortality in a number of different features that we discussed. We use these calculators, both at the time of diagnosis and in follow-up, to risk stratify and really define how aggressive we need to be with treatment.

**Dr. Mayeux**: I also find that the important part to remember with these risk calculators is that these are for phenotypically clear-cut patients. Bringing patients into those conversations about what our expectations are for their treatment and how we are going to watch them over time. I really like the visual of being able to present that information, particularly with the colors, with our patients in clinic.

**Dr. Waxman**: I think another nice thing about the risk calculators and being able to show a patient where they fall into these risk groups is to be able to lay the groundwork for talking about what are typically fairly complicated therapies.

## TREATMENT OPTIONS

### GENERAL MEASURES

**Dr. Mayeux**: Once we have risk-stratified our patients, we turn to our treatment planning. We have guideline-directed treatment and we know that our goal ultimately is to achieve and maintain a low-risk profile. For us, that may be a numbers game. For patients, that means that they can live a better life and that they can feel better. Clinically, we are looking to address the systemic consequences of pulmonary hypertension and right heart failure and avoiding the risk of heart failure.

We'll talk about medications in a moment, but in regard to general measures, these are the everyday things that we are doing for our patients that are not specifically directed therapies. Physical activity is incredibly important. Pulmonary or cardiac rehabilitation therapy can do wonders for our patients, getting them up and moving again. Think about the years that it takes for a patient finally to present with dyspnea to one of our programs or to somebody to get the diagnosis of pulmonary hypertension. There's likely been a huge cycle of deconditioning on top of the progressive changes in their cardiopulmonary status. Anticoagulant therapy was far more common years ago. It is definitely an individualized decision with potential risks and benefits. And there is some evidence of potential benefit, but maybe some potential harm in other types of PAH patients. So again, this comes down to patient-centered decision-making.


Diuretics are important. We know that our patients who are suffering with right heart failure oftentimes will be volume overloaded and with the RAAS activation, we may have more difficulty managing these patients. But with the use of diuretics, and potentially even fluid restrictions or figuring out sodium intake, we can really optimize these patients, making them feel better with diuretics as well as reducing that stress and strain on the heart.

To continue, there is not a lot of data to suggest that we should be using our typical cardiovascular medications, namely GDMT therapy that we would see in left-sided heart failure. Some of these therapies may contribute to hypotension or bradycardia which can be dangerous in pulmonary arterial hypertension. And then, as a side note, the PAH therapies, although they are not meant to cause systemic hypotension, they certainly can contribute to decreasing blood pressures.

Oxygen therapy is incredibly helpful because any time our oxygen levels really dip, we can have hypoxic vasoconstriction in the lungs, further contributing and worsening pulmonary hypertension and increasing volume overload. Optimizing somebody's oxygen therapy, including sleep studies, including looking at the oxygen levels at night, can be important. Fixing iron deficiency can certainly be of symptomatic benefit for patients and those who are anemic certainly should be replenished. Vaccines to help prevent additional illness. We know that our patients have a lower threshold to be able to easily stroll through some of the commonly acquired viral illness, and vaccination can certainly help prevent unwarranted hospitalizations and morbidity. Psychosocial support throughout this whole process can be given by all of us as providers, through more formal social networks or social workers in clinic. There's a lot of support available in the community for PAH patients. And then, lastly, we need to do a lot of counseling about pregnancy risks, as well as contraception, when we are thinking about using our teratogenic therapies, particularly ERAs or SGCs.

## Pathway-Specific Directed Treatment and Initial Risk Stratification

Let's talk about those therapeutic pathways. There are 3 therapies that were considered pulmonary vasodilators. Even though we know that these therapies do more than just vasodilate, they have some other potential benefits and inherent properties. They have been our mainstay of therapy, particularly dual up-front combination therapy with the therapy in the endothelin pathway, as well as in the nitric oxide pathway. With those therapies, the goal is to vasodilate, open up the blood vessels in the lungs essentially, to reduce pressures. There is some potential for increased or decreased inflammation and decreased fibrosis maybe, but enter into 2024 we have a new therapy which is pictured on the right-hand side which is the activin signaling pathway where we can actually see that there is a change in the proliferation of cells in the pulmonary arteries with the hope of improving that right heart function by decreasing the pressure in the pulmonary vasculature.

How do we know what to do? We now have several therapies that are FDA-approved for the treatment of pulmonary arterial hypertension, and the initial treatment is really dependent upon those without cardiopulmonary comorbidities. Those who have pulmonary hypertension and other comorbidities, particularly significant lung disease or heart disease, really need to be managed carefully and closely, and potentially at an expert center because some of these therapies have been shown to be harmful. Many of them haven't shown to be of any benefit, so they're not clinically recommended. But it's really important to have follow-up assessment and individualized therapy for those patients who are considered to have comorbidities associated with their pulmonary hypertension.

Now, for those without cardiopulmonary comorbidities, we use our risk stratification. And our patients who are low, intermediate or high risk get 2 oral therapies right out of the gate, and then the conversation about additional therapies with regular follow-up. I know that some programs will see patients more frequently than every 6 months, particularly in that early stage, to get a good handle on response to therapy or side effects of therapy. Our high-risk patients, we really know we need to be aggressive with, again using that dual up-front oral therapy, but also with parenteral therapies, namely intravenous or subcutaneous prostacyclins. And the follow-up assessment is again important and at a specific interval, depending on how patients are doing.

Let's talk about the pathway-specific treatments. We're going to talk about the phosphodiasterase inhibitors. These


are our PDE5s as the abbreviation. Those agents are known as sildenafil and tadalafil. Sildenafil is available in an IV formulation, but we don't use that on an outpatient basis. It's oral 3 times a day. Tadalafil is oral once a day. The side effect profiles are really similar, mostly body aches, headaches and maybe some diarrhea and flushing, but typically those side effects are self-limited, initially. We're going to talk about soluble guanylate cyclase agonists. There is 1 therapy available right now, that is 3 times a day and the same type of profile except it seems that hypotension and reflux tend to be more common with riociguat.

When we are talking about our really sick patients, we need to be thinking towards prostacyclins, and maybe they will be started initially, if we're meeting them as a new patient, or will be started fairly soon after that initial heart catheterization. They include medications like epoprostenol or treprostinil which can both be delivered intravenously. These are pumps that patients are wearing 24 hours a day without a plan to interrupt therapy. Treprostinil can be delivered via an inhaled route 4 times a day or subcutaneously, again smaller pump, 24 hours a day. Many of the vasodilators have the same side effects, headaches, body aches, potential for nausea. The parenteral therapies have more diarrhea, as well as our prostacyclin receptor agonist, selexipag.

Overall, these are patient-guided discussions or we guide patients through these discussions to decide what therapies do they need to recover their heart function or preserve their heart function as well as what is realistic for them and what is safe for them.

Going back to the endothelin receptor antagonists, we have 3 options of varying age, and these therapies are more likely to cause a little bit of anemia than the others. And lastly, our fourth or newest pathway of therapy, the activin signaling inhibitor known as sotatercept, which we'll talk about, has a unique side-effect profile.

### Activin Signaling Inhibitors

Sotatercept was studied initially in PULSAR and then STELLAR which was its phase 3 clinical trial. These studies were 24-week trials for patients and placebo-controlled. All of the patients on sotatercept were already on background therapy, so nobody was naive to pulmonary hypertension therapies and, to be honest, this was a fairly well-treated population. The majority of patients were already on 3 background therapies, many of them on pump therapies, so prostacyclin agents, either subcu or IV, and many of them on oral prostacyclins as well. These patients got randomized to either sotatercept or placebo.

Sotatercept is a subcu injection that is given every 3 weeks. The initial dosing was a smaller sort of starter dose and then 3 weeks later, as long as hemoglobin was okay, patients were transitioned to a weight-based of .7 mg/kg and they stayed on that schedule every 3 weeks.

The primary end point, of course, was change in the 6-minute walk test, like the majority of our other PH therapies. We were also able to see an improvement in PVR and NT-proBNP. Many of these patients did have some sort of adverse event and all of the pooled analyses were positive as far as end points were concerned, with sotatercept.

SOTERIA is going to give us a longer extension of patient side effects and reported outcomes, for sure. Patients who are in this study can stay in it for many years, so we are currently working through some of the interim data with SOTERIA as well. The majority of patients had some sort of treatment effect or side effect, but very few, overall, discontinued treatment, with about 3.8%, because of some of the side effects, namely decreased platelet counts and moderately to severely increased hemoglobinemia. Patients had to decrease their dosing or dose hold in order for those numbers to improve. With sotatercept, there is an increased risk of thrombocytopenia, yes, thrombocytopenia, and then high hemoglobin levels. Patients, particularly those who are at high elevation that I work with, we are really watching them very closely for this increase in hemoglobin and, at times, it'll be so high we'll have to dose hold. Other risks include the development of telangiectasias and bleeding. The bleeding typically reported are nosebleeds, but there is a risk for GI bleeds as well and to the point that they're severe enough that patients have had to come off therapy for them. It is a wonderful new target. It is fantastic that we have new data and a new therapeutic pathway for patients, but there are some risks that are different than our vasodilator therapies.


### Clinical Development

Moving on, we know that there are more therapeutic targets in development. There are phase 2 and phase 3 trials. More recently, seralutinib will be reported out and that is our phase 3 trial. We're again looking for patients' improvement in 6-minute walk distances. Satralizumab is a phase 2 study looking at multiple types of pulmonary hypertension with this IL-6 response which is a new therapy as well. More agents that are coming, a liposomal treprostinil inhalation suspension product is being trialed. That will decrease the burden of 4 times daily inhaled treprostinil therapy as well. Ralinepag is a prostacyclin receptor agonist, similar to the mechanism of action of selexipag. That is also in a phase 3 trial and we're waiting for those outcomes. And then, another SGC being trialed as well, again looking at 6-minute walk distance outcome in a 24-week period.

### Key Concepts

Our key concepts, of course, treatment goals are to maintain and achieve this low-risk profile that Dr. Waxman has talked about. Another goal is to just consider all of the other things that we can do that can make our patients' lives better, that we can decrease strain and stress on that heart. So, diuretics, oxygen, maybe anticoagulation if that's appropriate, absolutely rehab, fixing all of the other comorbidities or improving the other comorbidities that may be contributing and then really honing in on selecting appropriate therapeutic pathways. Dr. Waxman, one of my questions for you is what targets and what future therapies are you most excited about seeing in pulmonary hypertension?

**Dr. Waxman**: That's a great question. I think 1, a lot of the drugs we have now are probably underutilized, and being more aggressive with up-front combination therapy is really important, especially if we're going to try to improve that low-risk profile goal. As far as most exciting to me are, right now, the activin inhibitors and, right now, sotatercept being the first generation. There are additional activin inhibitors being studied that may have improved ligand engagement and maybe even better outcomes which have been quite spectacular. And I think fundamentally these newer drugs that you mentioned, many of which are not just primary vasodilators but actually target specific growth factor pathways, inflammatory pathways may actually, in combination with the activin inhibitors, turn out to have real disease-modifying effects so that we can, maybe in the future, even simplify our patients' treatment.

## COMBINATION THERAPY

### Follow-Up Risk Stratification

**Dr. Waxman**: Importantly, we've already touched on some of the steps we take to risk-stratify a patient in hopes of deciding how best to treat that patient. And initial risk assessment is often the first step, and we can divide our patients into a high-risk category and not high-risk and that will help us decide how aggressive to be up-front. And it comes down to 2 agents at a time, 3 agents at a time and now 4 agents at a time and being able to modify those therapies, depending on the patient's needs.

As we follow the patient, once we've initiated therapy, we do a secondary risk assessment and that gets to the 4-strata risk categories. And here again we can decide to intensify treatment, depending on has that patient moved down to a lesser risk category or are they still at this high-risk or intermediate high-risk category where we have to consider 3 agents and even consider adding a fourth agent. And again, we have our targeted therapies in the prostacyclin pathway, the endothelin pathway and the nitric oxide pathway involving both the phosphodiesterase-5 inhibitors and the soluble guanylyl cyclase stimulators and now adding in the fourth pathway being the activin signaling inhibitor pathway.

There's a fair bit of data over the years that supports the use of combination therapy and, quite frankly, I think if we consider any complicated disease in medicine, we would never consider treating any complex disease with just a single agent and that's true for PAH as well as any form of heart failure, HIV, cancer, you name it and we do combination therapy. The initial consideration for combination therapy came up now almost 10 years ago with the AMBITION trial where we looked at the combination of ambrisentan and tadalafil, a PDE5 inhibitor and an ERA, up-front, at the time of diagnosis vs each agent as a monotherapy. And we saw very clearly that there were improvements in long-term outcomes, reduced hospitalizations and better efficacy. There have also been some meta-analyses to confirm those findings. And even more recently, there have been some additional studies


similar to AMBITION that have replicated those results, supporting the role of combination vs monotherapy.

### Treatment Escalation

The whole concept of treatment escalation gets to risk assessment and prognosis. We start patients off at the time we meet them and, again, hopefully making that decision based on their risk assessment and then those follow-up visits, and for our center, we generally will follow a new patient up at 3-month intervals until we know that they're getting better because we want to make sure we don't let them fall through cracks and, if they're not moving down a risk category, we want to intensify therapy and that could mean moving to triple combination therapy and even to the fourth agent, that being sotatercept, an activin inhibitor pathway.

As far as how we optimize that combination therapy, I think importantly, right now, there's no right answer as to what treatment to start on in any individual patient. We have not really reached the age of personalized medicine. Hopefully we will soon, and you need to be willing to try up-front choices after a good discussion with the patient and then being willing to change those drugs around, depending on how the patient responds. That could mean adding an additional agent on, it could also mean switching within classes, such as switch sildenafil for tadalafil, because some patients definitely respond better to individual agents than others.

Other things to consider, when we add them on, the strength of evidence is pretty good as far as adding on an ERA to a PDE5, although again up-front combination would really be ideal. Also adding on an oral prostanoid, such as selexipag or oral treprostinil, to background dual combination therapy has been shown to improve the patient's risk category. We use exercise tolerance as a measure of when to do this. You can use either a 6-minute walk test or an exercise test, such as cardiopulmonary exercise test, and we've got a fair bit of data that show when we combine certain drugs, like PDE5s and prostacyclines, they have additive, if not synergistic, effects.

As far as the real-world outcomes in managing this disease, there's clearly a significant unmet need. Many patients, in spite of us developing all these new therapies, still are being started on monotherapy and there's been significant delay in adding on or utilizing combination therapy. We know now that add-on sequential therapy is really a delay in optimal therapy and up-front combination should be the standard of care. Treatment escalation has been shown repeatedly to really lower that hospitalization rate and certainly re-hospitalization rate. And with aggressive up-front combination therapy, we can even see significant improvements over time in hemodynamics and right heart function.

One of the important questions that has come up since the advent of sotatercept and targeting the TGF-beta signaling pathway and activin inhibition, is when should sotatercept be introduced. The ZENITH trial asked the question of those patients who have advanced disease—so those who remain a functional class III or IV in spite of aggressive combination background therapy—will sotatercept be beneficial? This was a phase 3, randomized, double-blind, placebo-controlled trial that looked at patients who had had disease for quite a long time, the majority of patients had had disease for upwards of 7 years, and remained significantly impacted by that disease. We used the same treatment approach as in the STELLAR study, starting patients at 0.3 mg/kg and, after 21 days, increasing to 0.7 mg/kg. And then we followed patients out for 6 months.

What we found was that there was a very significant benefit. We actually stopped the trial early at a predefined interim analysis because the efficacy was so significant. The primary end point was composite of all-cause mortality which is actually a higher bar to set than just PAH-related mortality or lung transplantation or hospitalization for worsening PAH. There was significant improvement in those patients treated with sotatercept vs placebo. And this is actually one of the first studies that showed a lower risk of death from any cause in PAH.

### Key Concepts

I'm hoping we've gotten the point across that combination therapy is really fundamental and really is probably the 1 thing that has had the biggest impact on improving outcomes in our patients over really the past 10 years. The treatment escalation is now detailed in the guidelines that Dr. Mayeux had actually talked about at the beginning of this presentation, published in 2022 by the ESC and ERS. And hopefully the data is convincing that sotatercept, as an


add-on therapy, is highly effective and well-tolerated in these patients.

**Dr. Mayeux**: Dr. Waxman, because we are moving in this age of patient-centered decision-making, how do you typically present options to your patient?

**Dr. Waxman**: I go over their risk assessment in clinic. I talk to them about all the classes of drugs that we've developed. I do explain that what drug might be best for them is more a trial and error process, but that there's no question that they need to be on a combination of different drugs. For patients who are functional class IIs and IIIs, especially early IIIs and who are intermediate, high or lower, we'll talk about dual and maybe triple combination therapy. I think patients who are in advanced functional class III and IV, we do talk aggressively about IV therapy as their primary option, then quickly adding on oral combinations. Usually, we'll start with a PDE5 after initiation of IV prostacycline and then an ERA, just so we can separate out the side effect profiles and make sure we can get the patients tolerating those drugs. And if they're still symptomatic after 3 to 6 months from that, that's when we start to talk about sotatercept, and we do take patients back to the cath lab if we're going to be starting sotatercept. We make sure that they are still in a range and truly symptomatic because of pulmonary hypertension.

Well, I would add here too that when we talk about sotatercept, one thing we bring up, especially in our patients with scleroderma who already have significant telangiectasias, one of the important side effects of sotatercept is development of or expansion of telangiectasias which can cause some bleeding complications. We do want to make patients aware of that and we have had some patients, I would say, shy away from sotatercept, although it's a rare patient, but the bleeding risk is real.

## PERSONALIZING TREATMENT

### Personalizing Treatment Goals

**Dr. Waxman**: I think one thing that is becoming increasingly clear in medicine is that we're striving towards a personalized approach. We're not really there from a molecular standpoint in pulmonary hypertension yet, but there's certainly personalizing of treatment goals in this disease and helping patients make decisions about complicated treatment regimens. I think, importantly, we want to establish some clear short- and long-term goals of treatment. When we meet patients, we often tell them our goal is to make them a functional class I if we can, so really decreasing their symptom burden as much as possible while, at the same time, managing side effects. We do strive to individualize the approach to treatment. We consider patients' comorbidities, especially our patients with connective tissue disease or some underlying cardiopulmonary disease that may be subtle. We want to make sure that they're tolerant of any symptoms and that we give them some clues into how to manage any side effects of these medications. And our team has really figured out how to manage many of the side effects so that patients can stay on drug. And then supportive therapy, really managing the day-to-day aspects of any patient with heart failure, like volume management and pain and their shortness of breath.

### Phenotype and Genotype Evaluation

As far as phenotype evaluation, really detailing the features of an individual patient is key, looking at what are their comorbidities, do they have idiopathic disease or is it associated with something like connective tissue disease. We've learned from studies like the registries in Europe, COMPERA, ASPIRE, as well as REVEAL in the United States, and most recently the PVD OMEC study in the United States, that lots of patients come with lots of different features of disease that do make treatment decision-making a little more complicated. We really want to make sure we define that patient population. Are they a specific group, like the WSPH group I disease, PAH, which was talked about at the very beginning, or might there be some overlap with group II, as they get older maybe group III in patients, especially connective tissue disease, who have some underlying lung disease? What is the functional class? Many patients present to us as functional class IIs or IIIs. Not long ago, most of our patients presented as functional class IIIs and IVs, so we are getting better at recognizing these patients earlier. And then, the important thing here is survival and improving that as we start to phenotype these patients and detail a treatment algorithm for them.

Once we make a diagnosis, I think making sure that the diagnosis is correct and does that diagnosis have any impact on family and offspring. Certain groups of patients, like the familial patients or heritable patients, patients with


PVOD, which is pulmonary veno-occlusive disease, or pulmonary capillary haemangiomatosis, some understanding of a genetic basis. We will consider genetic counselling in those patients and even do genetic testing. One caveat to that is oftentimes insurance may not cover genetic testing, but it can be important to inform a patient, as well as inform their family, if there is concern about risk of disease. Oftentimes, that won't impact how we treat a patient, but it will certainly impact how we might follow patients and their family members, especially if they're asymptomatic carriers.

### Interprofessional, Multidisciplinary Approach

Now, one of the most important things that has evolved over the years is the idea of this being an interprofessional/multidisciplinary disease process and it really requires collaboration among a number of different subspecialties. I think the Pulmonary Hypertension Association care centers have really promoted this whole concept. If we think about the disease itself, it automatically often involves cardiologists and pulmonologists. It clearly involves primary care providers and it involves rheumatologists often. Part of that team are also the advanced care providers who often manage the day-to-day work of taking care of these patients. I know, in our program, we would be lost without our advance care providers. Really being able to use this unified approach to explain the disease, its diagnosis and management to patients and help them make the best treatment decisions they can and also being able to follow patients closely and make sure that we can make adjustments in those treatment plans, especially if side effects should come up or if there are complications of their disease.

The care coordination really involves communication, both between the providers, the family and even the ancillary services that are required, like the home care nursing services that we rely on, especially in our patients on advanced therapies, rehab programs that patients might get involved with, exercise programs and even transitions when a patient is in hospital to going back home. And I think, importantly, taking into consideration those patient goals and how to integrate into both the initial and subsequent selection of various therapies. Obviously, a patient needs to be able to handle those therapies, understand those therapies and utilize those therapies in the most effective way. We need to also keep an ongoing assessment of disease burden and quality of life. As we've mentioned over and over, these treatments are quite complicated for many patients, and we don't want to saddle an already cumbersome disease with a cumbersome treatment ordeal.

And then there are organizations and resources that we need to make our patients aware of. I think most importantly the Pulmonary Hypertension Association has been fundamental in supporting patients and getting them the best care they can. And, in fact, their website is a great place to go to learn more about the disease and also learn about where care may be available.

### Key Concepts

Just to touch on some key concepts, again inviting Dr. Mayeux back to talk through this, I think this is clearly an individualized treatment system that really requires an understanding of patient-specific goals as we design that treatment plan for each patient. As I mentioned, a lot of coming to those decisions is doing a very thorough phenotype and maybe even a genotype of the patient so that we can really explain the recommendations we're making in a clear manner for the patient. And then I think, as I hope I stressed, the interprofessional/multidisciplinary approach is really key for not only optimizing but improving the disease management for these patients with pulmonary hypertension.

**Dr. Mayeux**: I agree, and I think the Pulmonary Hypertension Association has done an incredible job of bringing not just physicians and advanced practice providers together, but also including respiratory therapists, pharmacists, registered nurses, that whole collaborative model that it takes to get this train running down the track just fine. And then providing that individualized treatment for patients. There are definitely patients who will tell one person one thing and another member of the team another and coming together to collaboratively help those patients makes a big difference, both for the patient as well as our satisfaction for the job.