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Pulmonary Arterial Hypertension: Screening, Diagnosis, and Optimizing Management

**Annoucer Open:**
Welcome to CME on ReachMD. This activity titled: Pulmonary Arterial Hypertension: Screening, Diagnosis, and Optimizing Management, is provided by Clinical Care Options, LLC and is supported by an independent medical educational grant from Merck and Company. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

**Dr. Kesler:**
Welcome to today's continuing medical educational webinar titled; Pulmonary Arterial Hypertension: Screening, Diagnosis, and Optimizing Management. My name is Sarah Kesler, a Scientific Director with Clinical Care Options, and I'll be moderating today's session. This webinar is jointly provided by Clinical Care Options LLC, and the program is supported by an educational grant from Merck and Company. Our faculty chair for this program is Valerie McLaughlin. She'll be giving our presentation today. Here are her disclosures.

Dr. McLaughlin is the Kim A. Eagle endowed Professor of Cardiovascular Medicine and the Associate Chief Clinic Officer of Cardiovascular Medicine in the Department of Internal Medicine at the University of Michigan in Ann Arbor, MI. Here are learning objectives.

So, with that, I'll turn it over to Dr. McLaughlin to start us off with a poll.

**Dr. McLaughlin:**
Great. Well, thank you so much. It's such a pleasure to be here. So, we have a couple of questions to start out with, and the first question is, in an average week, how many PAH patients do you take care of? So, I'll give you a little bit of time to answer.

Okay. So moving on to the next question, and that is; Based on the 2022 ESC/ERS Guidelines, a peak tricuspid regurgitated velocity of 3.5 meters per second is indicative of what? So, low probability of PAH, intermediate probability, or high probability? I'll give you a few moments to answer.

OK, let's see what everyone thought. So about half intermediate, and about 40% high. So, OK. We will talk about that.

The next question is an individual is newly diagnosed with PAH. Their REVEAL 2.0 score is 12, which is a high-risk score, and they are non-vasoreactive and have no comorbidities. Which of the following would be the best initial treatment, so, calcium channel blockers plus ERA, PRA with PDE5 inhibitors, ERA with PDE5 inhibitor and a parenteral prostacyclin therapy, and/or would it be oral monotherapy with either a PDE5 inhibitor or an ERA? So go ahead, vote.

OK, and let's see the responses. So, wow, that's, pretty even distribution amongst the last three. The correct answer is triple therapy, and I'll talk about that in the treatment algorithm.

And then, one more question. In the Phase 3 STELLAR trial, which emerging therapy resulted in a greater improvement in exercise capacity compared to placebo for patients with PAH receiving stable background therapy? So, was that MK-5475 or erlotinib, seralutinib, sotatercept. And so, go ahead and vote.

Ok, let's see what everyone thought. OK, so seralutinib and sotatercept have the most votes and the correct answer to that is sotatercept, but I'll talk a little bit about that trial during the course of our discussion tonight.

So, let's just start by discussing the evaluation and diagnosis of patients with pulmonary arterial hypertension or pulmonary hypertension. And its sort of a really challenging diagnosis to make because the symptoms are so non-specific. I'm sure all of you see patients with exertional dyspnea every day in clinic, and there are a lot of other causes that are much more common than pulmonary hypertension.

There are some things in their medical history that should raise the suspicion of pulmonary hypertension, including a family history. Some of our cases are inheritable in nature. And there are some diseases that are associated with a higher incidence of pulmonary arterial hypertension, such as scleroderma. But that medical history, that persistent dyspnea on exertion, was really the most common symptom.

The physical exam for pulmonary hypertension can be subtle in the early stages, but in patients who have more significant pulmonary hypertension, you listen for that accentuated pulmonic component of the second heart sound. Really hearing that loudly over the apex where you should hear the first heart louder. Patients in RV failure you might hear a right ventricular third heart sound. Many of our patients have the systolic murmur of tricuspid regurgitation, but some of them even have the diastolic member of pulmonic regurgitation. When they're in heart failure you might see a high JVP, peripheral edema. Um, sometimes they're cyanotic, either because they have lung disease or they a shunt. So, those are important physical exam findings.

A number of diagnostic tests are necessary to go through the evaluation. Now, certainly on laboratory studies you might find high biomarkers NT-proBNP or BNP reflective of strain on the right ventricle. Often on EKG, they have right axis deviation. Sometimes they're hypoxic. And then, you know, in patients with shortness of breath we often look for lung etiologies and heart etiologies, so some of the pulmonary diagnostic testing includes PFTs. We'll often see a reduced diffusing capacity. The chest X-ray might show enlarged central pulmonary arteries and pruning of the peripheral vasculature. A chest CT might also appreciate that enlarged pulmonary artery and often enlargement of the right heart chambers as well. And on the ventilation perfusion scan, what we're looking for is evidence of chronic PE, which is, of course, a very unique type of pulmonary hypertension.

The Echo really is the cardiac diagnostic test that's on order early on and it gives us such important information. Of course, everyone focuses on the RVSP. You know what is the RVST? But I really want to emphasize that that's only one part of the Echo. There's so much other information to be gleaned from the Echo, including the size and function of the right ventricle, the size of the right atrium, the motion of the interventricular septum, some Doppler indices of right ventricular dysfunction, the presence of a pericardial effusion, are of course, prognostic indicators. And of course, the Echo is really critical to look for what really is the most common cause of pulmonary hypertension that we all see, Group 2 pulmonary hypertension, either LV systolic or diastolic dysfunction, or value of heart disease. And of course, if there's a high index of suspicion for that very unique Group 1 pulmonary arterial hypertension that's often best managed in concert with a center that specializes in pulmonary hypertension.

This next slide shows the updated clinical classification of pulmonary hypertension. This was published as part of the 2022 ESC/ERS guidelines, and it updates some of the discussion at the World Symposium, the 6th World Symposium event. So, Group 1 is pulmonary arterial hypertension, that very classic variety is what we used to call primary pulmonary hypertension. We now call that idiopathic pulmonary arterial hypertension. A small proportion of those patients might respond to acute vasoreactivity testing and actually go on to do very well with calcium channel blockers. A very small, but privileged group. And so, they divided – they added the non-responders and acute responders to vasoreactivity testing to the sub classification of idiopathic PAH. A pretty rare disease.

Heritable PAH is – you know, presents very similarly, but we diagnose that when someone has a family history. And of course, there are a number of genes that can cause this, which we can talk about a bit. Drug and toxin induced PAH is very important. We first recognized this many moons ago in the 1970s when there was an epidemic of PAH in Europe related to the diet pill aminorex. Some of you may have lived through the fun, fun epidemic. But now the most common drug-induced type of pulmonary arterial hypertension is related to methamphetamines.

And then there are some different diseases that can cause a higher incidence of pulmonary arterial hypertension. Probably the most common is connective tissue diseases. Patients with scleroderma have perhaps a 10 to 15% risk of developing pulmonary arterial hypertension. PAH is more common in HIV infection than the general population, not as common in scleroderma, so maybe 0.5 to 1%. But it's something to think about in a patient with HIV who has dyspnea, and you can't find another reason for it.

Portal hypertension is important to recognize because of the risk of pulmonary arterial hypertension at the time of liver transplantation in patients who are candidates for that. So, these patients get very aggressively screened as part of the transplant work-up.

Congenital heart disease. These patients are living longer now. I'm sure we're all seeing them. We're seeing patients who are palliated or repaired at younger ages that are now living into adulthood because they're doing so much better, and some of them may have some kind of residual of their congenital heart disease. And occasionally, we find a patient that, you know, that the congenital heart

disease was missed, and they present as adults. And sometimes even patients who have congenital heart disease that's just repaired too late. So I think it's really important to keep that in mind. Schistosomiasis can also cause pulmonary arterial hypertension, not a problem in the US, you know, mostly in South America and sub-Saharan Africa. And then there are a couple unusual variants that really involve the vein, the pulmonary veins and the pulmonary capillaries, so PVOD and PCH. Um, and that's what we're really going to focus on most today. But as we go through the diagnostic algorithm, it's important to acknowledge the other types of pulmonary hypertension, which are actually much more common.

So, the most common type of pulmonary hypertension is that due to left-heart disease. And I think in all of our pulmonary hypertension clinics, we see a lot of patients with HFpEF. So now, the EF is normal, and we see high pulmonary pressures, but they have lots of risk factors for diastolic dysfunction and high left-heart filling pressures when you have them. So, it's really important to recognize that. I think people appreciate reduced LV function and valvular heart disease just because it's more obvious on an Echo. Any type of lung disease that causes hypoxemia can cause Group 3 pulmonary hypertension. Group 4 pulmonary hypertension is that associated with pulmonary artery obstruction, so that's most commonly chronic thromboembolic pulmonary hypertension. And it's really critical to distinguish that from one, pulmonary arterial hypertension, because the treatment is so different. And then of course, Group 5 is really a potpourri of things with unclear multifactorial mechanisms that can cause pulmonary hypertension.

So, the current definition of pulmonary hypertension is listed here. So, precapillary, or Group 1 pulmonary arterial hypertension, is a mean pulmonary pressure greater than 20 with a wedge pressure that's less than or equal to 15, and a calculated pulmonary vascular resistance of greater than 2 Wood units. Um, and so, patients with Group 1 PAH have to have this, but patients with Group 3, 4 and 5 can also have hemodynamics that are as described there. Isolated postcapillary pulmonary hypertension is basically Group 2. So, the left-heart filling pressures are high, but the transpulmonary gradient is normal and the pulmonary vascular resistance calculates to normal, so that's Group 2. But as we all know, there are some patients who have Group 2 pulmonary hypertension that for whatever reason develop this reactiveness and their mean pulmonary pressure is high and even though their wedge pressure is high, they're transpulmonary gradient is elevated and their pulmonary vascular resistance is greater than 2. And we call that combined pre- and postcapillary pulmonary hypertension.

And then in the ESC/ERS guidelines, they added back exercise PH. This has been in and out, and in and out, and they added it back. But they did it a little differently. They which I think is good, actually. Rather than saying just mean PA of greater than 35 with exercise, they really emphasize the slope of the mean pulmonary artery pressure over cardiac output. Because if your cardiac output goes up a lot with exercise, your mean PA might go up a little bit too. But your PDR might go down. So really that ratio is important.

So, I've already highlighted the types of Group 1 pulmonary arterial hypertension and here now are some of the heritable causes. We've made so many discoveries of different genes that can cause heritable pulmonary arterial hypertension. The most common is the BMPR 2 mutation but a number of other mutations have been identified. And I think it's really important to discuss what patients might be appropriate for genetic testing. Of course, patients with heritable PAH we often find a gene. Not always, but often. But actually, we find a lot of mutations in patients who have IPAH and don't have a family history. And whether they're spontaneous mutations or whether it's because the the gene has incomplete penetrance and we really are challenged with the family history, it's unknown. But we do offer genetic testing to not just our heritable patients, but also our idiopathic PAH patients. And genetic testing is really important to consider. Patients should be seen by a genetic counselor to really understand the implications of genetic testing, and there is a whole panel that will look for all of these common genes that are associated with pulmonary arterial hypertension. And if somebody tests positive for a pathogenic variant, it doesn't necessarily mean that they're going to develop the disease. As I said, most of these diseases don't have full penetrance. You know, perhaps only 20% of patients with the gene actually develop the phenotype. So, one of the important things to council patients who have the gene is to just be aware of symptoms and to try to seek medical attention early should they develop any of the symptoms of pulmonary hypertension.

Group 2 disease, again, very common. And I really love this figure from the ESC/ERS guidelines that really go through the different types of left-heart disease that can cause pulmonary hypertension. So, HFrEF, HFpEF, even heart failure with midrange EF and then left-heart valvular disease, aortic or mitral valve disease. And as I said, most patients with left-heart disease don't develop severe pulmonary hypertension. But some patients for whatever reason develop this pathogenic vasoconstriction where they get remodeling of the pulmonary vasculature, which can look very much like Group 1 PAH. Really develop, uncoupling of their right ventricle and PA and progress to have right ventricular dysfunction and pretty severe pulmonary vascular disease. It's a tough group to treat, these patients with combined pre- and post-capillary pulmonary hypertension because there's really no therapy that is FDA approved to treat that. So, it's really management of diuretics and the volume status and their underlying left-heart disease.

Group 3 pulmonary hypertension. Similarly, we see many patients with lung disease who have pulmonary hypertension. You know, most patients if they have pulmonary hypertension, it's not very severe. But again, for whatever reason, you know, whatever predisposition they have, a small proportion of patients with either COPD, ILD, or combined pulmonary fibrosis and emphysema

syndrome develop more severe pulmonary hypertension. And that's also difficult to treat and sometimes even treating the pulmonary hypertension doesn't have a huge impact on their symptoms because of many of their symptoms are caused by their underlying lung disease.

Group 4 pulmonary artery obstruction. I can't emphasize enough how important it is to make sure you evaluate this because this is a potentially curable cause of pulmonary hypertension, and you don't want to miss it. So, if you have a patient with unexplained dyspnea and evidence of pulmonary hypertension, whether or not they've had a PE, it's important to do a ventilation perfusion scan. That is the study of choice to exclude chronic thromboembolic pulmonary hypertension, and of course, most of these patients will have an echocardiogram as well. If the ventilation perfusion scan is abnormal, it is really important for the patients to be fully worked up for chronic thromboembolic pulmonary hypertension, which is usually best performed at a center that specializes in CTEPH or PH. And it really is important to do a right-heart catheterization and pulmonary angiogram to understand the anatomy. And of course, once you do that it's very much like the heart team for valvular heart disease these patients need to be assessed by a multidisciplinary team at a CTEPH center to understand their anatomy, their hemodynamics, you know, what the ideal way to revascularized them is, either surgery or BPA if they're candidate for revascularization or medical therapy. So that's a little bit about the classification, the different ideologies.

This is a very old slide, but I think it's really, very illustrative of what happens to the pulmonary vasculature as one develops pulmonary hypertension. So, on the left you see a normal pulmonary arterial that is into the median, nice big lumen. And then in the middle you see the beginning of pulmonary hypertension where you see smooth muscle cell hypertrophy, intima proliferation. You see barreling of the lumen. And then as the disease progresses, you can develop further vascular narrowing. You can see why the resistance is climbing. You might even develop these plexiform regions, that's the classic microscopic finding of pulmonary arterial hypertension.

So, as I said earlier, one of the reasons this disease is so difficult to diagnose is because the symptoms are non-specific. You know, probably more than three-quarters of the patients present with dyspnea on exertion, a very nonspecific symptoms. Many of them also have fatigue, exhaustion, what we refer to as bendopnea, you know, dyspnea when bending over, palpitations. Hemoptysis is typically a later sign. Sometimes people have abdominal distension, fluid retention. Syncope is a very bad sign that can often occur during or shortly after exercise. And it's really impaired flow to the brain because you just have such a high resistance. You can't manage a cardiac output with exercise. So, you'll – and then, positional chest discomfort can occur because of a proportion of the main coronary artery even pulmonary artery. Sometimes you can get hoarseness because of compression of the left pharyngeal nerve on – Sorry, I'll try to speak a little bit louder. And then atelectasis wheezing can occur because of compression.

Here this is also from the ESC/ERS guidelines. These are the clinical signs of pulmonary hypertension. So, we talked a little bit about this earlier, that loud P2, that TR murmur or that PR murmur are really the most common physical exam signs. Of course, the signs of right heart failure you're all very familiar with. So, distended abdomen, ascites, lower extremity edema. Of course, you might see signs pointing to other causes of pulmonary hypertension, like flooding in a patient with cyanotic congenital heart disease crackles in patients with pulmonary fibrosis evidence of DVT's, telangiectasias in patients with scleroderma.

Now, this is the diagnostic algorithm from the ESC/ERS guidelines. I'm going to be honest; this is not my favorite diagnostic algorithm that's ever been published. I think this is written more for a general practitioner who is faced with a patient who has symptoms of dyspnea. Maybe some physical exam findings and it basically says do you want to go down the lung disease pathway or do you want to go down the heart disease pathway? And in reality, we're often doing those two things concurrently. It does highlight that in a patient who has very concerning findings for Group 1 pulmonary arterial hypertension or CTEPH, that they should be referred somewhat urgently to a PH Center of Excellence.

Now, this is probably my favorite figure from the ESC/ERS guidelines, and this, I just want to laminate this and put it in every Echo lab there is because this is it really shows the importance of all of the other findings besides the PASP on echo that need to be evaluated. And so, it gives some of the 2D findings in the different view, so it looks at right ventricular size, right ventricular function. In panel C, this is one of the most important images I like to look at is the short access through the ventricle and it really tells you the interaction of the right and left ventricle. It's where you look for that right ventricular pressure overload, the RV outflow tract acceleration time is really critical. It's SP RVS prime. But a lot of Doppler indices that can help you assess RV function objectively. The right atrial area, the amount of TR, these are all important findings on the Echo, in addition to that healthy SP.

So, I think it's really critical to look for all of these findings. And the other figure from the guidelines that I think is really nice that puts this in perspective is that the Echo, it has so much information. So, we don't make any decisions generally just on the tricuspid velocity because there's so much else to look at. The cut-points that they use for tricuspid velocity are less than 2.8 is the low risk, 2.9 to 3.4 is intermediate risk, and greater than 3.0 is high risk. So, if someone – actually greater than 3.4 is high risk. So, if it's greater than 3.4 we're probably worried about that patient, but we might be worried about the patient with a TR velocity of less than 3.4 based on some

of the other Echo findings, based on some of those images that I just showed you in terms of LV size and function. So, this helps you integrate the RVSP and the rest of the Echo findings, and it helps you decide whether or not you need to go on with a right heart catheterization. And again, that may be the case of the TR velocity is high, but it may also be the case if the TR velocity is not high, but you have some of the other Echo findings that make you worried. So, some of those patients might need a right-heart catheterization, others we might recommend a follow up Echo, and those who have no probability based both on TR velocity and the other findings, we might look for an alternative diagnosis.

Now, as much as we learn so much from the Echo, you have to have a right-heart catheterization to make the diagnosis of pulmonary arterial hypertension. Um, it's really critical to measure the left heart filling pressures. Again, diastolic heart failure is such a common cause of pulmonary hypertension, so we really need to have an accurate assessment of left-heart filling pressures. The are a number of calculations that we need to make. This is much more about how the heart functions, the cardiac output, than about the pressure in terms of the long-term prognosis. So, we get a lot of information about that. We look for shunts and we have to do the acute vasodilator challenge.

And this is a rather dry slide, but I think it really nicely lays out all of the measurements that are critical to obtain at the time of the right-heart catheterization. And this again is from the ESC/ERS guidelines. So, on the top, you see the pressure variables, the right atrial pulmonary artery and wedge pressures. You have to measure a cardiac output. That's often done using thermodilution and the saturations, and then you use that information to make the calculations. The pulmonary vascular resistance, the cardiac index, stroke volume, pulmonary artery compliance. All very important numbers.

Now, I think it's important to talk about vasodilator testing because we want to identify those groups who might respond to calcium channel blockers. It's pretty rare, but if you can find that patient, they are going to do – well, they are likely to do very well for a very long time with an inexpensive, well tolerated therapy. So, the drug that's used most commonly for vasodilator testing is inhaled nitric oxide. You just put it on 40 parts per million for about 5 minutes, and you get your answer rather rapidly. And we consider it to be a positive response if the mean pulmonary pressure drops by more than 10 to a mean pulmonary pressure of less than 40 without a decline in the cardiac output and without a rise in the wedge pressure. So, if a patient meets those criteria, they may respond to calcium channel blockers, and they can be treated with calcium channel blockers and then followed up to see if they have a clinical response. This is indicated for patients with idiopathic pulmonary arterial known hypertension. And even if you have a responder, it's important to follow that closely, as sometimes this response does not last indefinitely.

This is probably the best paper that's been written about this topic, and this looks at a large series in France where they looked at patients who responded acutely in the cath lab, and then were treated with calcium channel blockers. And then they followed the clinical response. So, patients who had an acute response that linked to tumors.Those who got better improved to functional Class 1 or 2 on calcium channel blockers without the need for additional therapies to add an almost perfect long-term survival. And then there was the other group who even though they had an acute response at the time of the heart catheterization, their symptoms didn't get better with calcium channel blockers. They didn't improve to functional Class 1 or 2. Yet, their survival was 4. It was really no different than patients who were not responders. So, it's really important that these patients be followed for a clinical response.

So, to just take this step back and summarize the diagnosis and screening, it's important to have a high index of suspicion. You know, unfortunately, patients get diagnosed too late. We have to go through this very thorough diagnostic evaluation. I really want to emphasize the importance of not forgetting chromic thromboembolic pulmonary hypertension. We have to evaluate for potential causes and contributing issues. It's really critical to have the right-heart catheterization. This is the only way you can make a diagnosis of PAH. And while it's not diagnostic, it's important to have a baseline functional evaluation to follow patients.

Now, in terms of managing patients, they come to us short of breath, they come to us not being able to go up the stairs or play with their kids and, you know, all they want is to feel better. They want less symptoms. But of course, as physicians, we want something that's a little more concrete than that. We want them to live longer. We want them to exercise better, and that’s uh, measured by the hall walk. We want to improve their hemodynamics and we want to keep them out of the hospital.

Now, like many other areas of cardiology, we have learned and learned about risk assessment, which helps us guide therapy. And there are a number of objective tools to help us calculate risk. One of the ones that is commonly used is the REVEAL Risk Calculator. This is based on the large US REVEAL Registry. Here’s the full calculator that includes both modifiable and non-modifiable variables, and you can see the scores are quite accurate at predicting 5-year risk. And there is a simplified version called REVEAL Light 2 that only uses 6 modifiable variables. So, those include functional class, hall walk, vital signs, biomarkers and renal function. So that is a tool that is often used.

And then, there also is a risk score based on the ERS/ESC risk assessment. This is the updated table from the ERS/ESC guidelines that goes through some of the predictors of risk. Really overlaps a lot with REVEAL; functional class, hall walk, biomarkers Echo, MR, the

LV function is really critical, and the hemodynamics predictors are really assessments of RV function. It's not PA pressure, it's LVRP is coping with that high resistance. And so, there's a simplified version that divides people into 4 strata; low, intermediate, low-intermediate, high or high risk, that uses just functional class, hall walk, and biomarkers. And they do this in clinic all the time. These are measurements that we get every single time we see a patient in clinic, and we have a smart phrase and a little file that we can just enter this data in, and it's spits out the risk status on our clinic notes.

And these are data from the CONCOR registry using that 4-risk strata that I think is really informative. And you can see how we can divide that intermediate risk group into intermediate-low and intermediate-high. On the left you see the risk status at baseline, on the right you see after therapy. And you know, really, response predicts response. Even if the patient has a higher risk status at baseline if we can improve them with therapy, they're to a lower status, they tend to do very well.

So, I've been so privileged in my career, I've been doing pulmonary hypertension – I hate to say it, but – for about 30 years now, and we have seen over a dozen therapies get FDA approved during this time and our patients have so many more choices and they get so much better and it's really wonderful to have access to all of these therapies. So we have agents that can block endothelin, which is produced at too high of a level in patients with pulmonary hypertension. We have two different types of agents that can modulate the metric oxide pathway, PD5 inhibitors and SGC stimulators.

And then we have a number of therapies that can modulate the prostacyclin pathway. There's a deficiency in prostacyclin in patients with pulmonary arterial hypertension, and we can either replace it with prostacyclin analogs, or we also have a prostacyclin receptor agonist.

And so, here is a list of the currently FDA approved therapies. There are a number of prostacyclin derivatives, epoprostenol, iloprost, and treprostinil which have different modes of delivery, including IV, sub - Q, inhaled, and oral. We have the one prostacyclin receptor agonist, selexipag. There are three endothelin receptor antagonists approved, besentan, ambrisentan and macitentan. There are two phosphodiesterase type 5 inhibitors that have been studied in, and they have the approval in Group 1 PAH, sildenafil and tadalafil. And there's one SGC stimulator, riociguat, which is unique in that it is approved for both Group 1 PAH, as well as chronic thromboembolic pulmonary hypertension.

Now, all of these medicines have side effects, and here are some of the common side effects. The endothelin receptor antagonists can cause volume retention. Occasionally you see anemia. Um, and they are iatrogenic and have to have monitoring through pregnancy. The PDE5 inhibitors headache and nasal congestion are common side effects, and some people get a fair amount of reflux symptoms with this as well. The proteinoids are very potent vasodilators and so we can see patients with headache, jaw pain, but they dilate the capillaries in the skin, so we see a lot of flushing and rash. It's important to consider the side effects that are associated with the different types of deliveries. So, line infections when delivered IV site pain sub – Q, cough for the inhaled forms. And the SGC stimulator side effects are quite similar to the PDE5 inhibitors, although tend to have a little bit more hypotension.

Now, this is the most recent treatment algorithm from the ESC/ERS guidelines. I will point out a couple of things that I don't think are great about this, but in general, it's a good treatment algorithm. Of course, it is important to have the correct diagnosis, and they want it confirmed in a PAH center. Appropriate patients should have vasoreactivity testing and, you know, some general measures. They divide this into patients without comorbidities on the left and with comorbidities on the right. So, that PAH patient without comorbidities should be assessed, and they emphasize those pretty strong at baseline. And for those patients who are at very high risk, they should have upfront combination therapy that includes a parenteral prostacyclin as well as an ERA PDE5. And for the patients who are at low or intermediate risk, they start therapy with an ERA and PDE5 inhibitor.

Now I think this is a little problematic because, as I showed you earlier, there's a difference between intermediate-low and intermediate-high, and I think there are some intermediate patients – there's patients with enough high-risk features that they should be getting more aggressive therapy that includes a parenteral proteinoid.

And in fact, in the text it actually says that, like, there's – there's an Asterix in the legend to this and in the text, it does say that, but it doesn't come out on the actual algorithm. And remember, this is just the first step. Our goal is to get people into low-risk status, so it's important to do a follow-up assessment and another risk store and there, they recommend that 4-stratum risk score at that first follow-up point. And if the patient is in low-risk score, with what you've done there is great, and they can continue there. If the patient is at intermediate-low risk, you know, we'd like them to be a little bit better, but they don't need the parental prostacyclin, the big guns, and so, they get the option of adding a prostacyclin receptor analog or switching the PDE5 inhibitor to an STC. There's a little bit of data on that. Um, but if the patient is at intermediate-high or high risk, they should have a parenteral prostacyclin added, if that hasn't been done already, or considered for lung transplantation evaluation.

Now, the patients at with comorbidities, they say they should start with just monotherapy with the PDE5. And, you know, I criticize this a

bit. I find that to be a nebulous statement here. What does that mean? A patient with a comorbidity could be a 45-year-old woman with heritable PAH and a PDR of 15 who's really pretty sick, who just happens to have hypertension or diabetes. I treat that patient according to the left category. Where a patient with comorbidities could be a 75-year-old woman with hypertension, diabetes, obesity, and when you cath her, you know, she's well-diuresed, her wedge pressure is 14, and her PVR is 3.1. To me, that's a patient with comorbidities that is probably not Group 1 PAH, even though their hemodynamics meet that criteria. And that's a patient I would treat with just monotherapy.

Now, despite the fact that we have so many drugs available, we're still losing patients. We don't get everyone to low-risk. And it's a very exciting time, there are more and more therapies being studied every day, and novel classes of medications as listed here. And there are no more investigational compounds right now. We'll talk a little bit about sotatercept even though the Phase 3 STELLAR has already reported out. There are a number of other trials going on in less ill and more ill patients. And then, the extension trial, there's an inhaled SGC being studied. There's a couple of inhaled tyrosine kinase inhibitors being studied. There's another oral prostacyclin receptor agonist, ralinepag seralutinib and then there's fixed-dose combination therapies as well.

I think the one that is furthest along is sotatercept, and this is a new mechanism of action. It's an activin signaling inhibitor. It works on the BMPR 2 pathway which really is a balance of anti-proliferation using the BMP 158. And pro-proliferation with activins and GDS. And so, what happens in some patients that is that there's a dysfunction at the BMPR2 receptor and so you get down-regulation of that anti-proliferation part of this pathway and then the pro-proliferation gets too active. And what sotatercept does is it binds down those activins and GDF's inhibitor for activin to reduce the pro-proliferative activity in this pathway and allow more anti-proliferative via the BMPR2 mechanism. And sotatercept was studied in a Phase 2 trial, PULSAR, with the primary endpoint of pulmonary vascular resistance, and that was reduced in patients who received one of two doses of sotatercept. And then it was studied in the Phase 3 STELLAR trial, and I think the remarkable thing about this trial is it was a trial of patients on current therapy. All these patients were on background therapy, many on triple therapy, many on parental prostacyclins. And even on top of that, there was a robust improvement in the primary endpoint of 6 -minute hall walk, and it hit the first 8 of 9 secondary endpoints as well, including time-to-death, or clinical worsening. So, a very impressive trial when you think about the totality of the data.

There's another trial going on, IMPACT, which is an inhaled lenvatinib. This is looking at patients with Group 1 PAH, again, on background therapies. And randomizing that to this dry powder version of lenvatinib or placebo, and the primary endpoint of this trial is 6-minute hall walk, and this is currently enrolling, it's currently recruiting. In the PROCERA study, which is another type of tyrosine kinase inhibitors, seralutinib, which is looking at a similar population of patients with Group 1 PAH on background therapy and randomizing them to seralutinib or a placebo. So, a very active clinical trial at this time. Seralutinib was already setting in the TORREY trial, the Phase 2 trial, which had the primary end point of 6-minute hall walk, and the Phase 3 trial is going on.

So I just also want to turn to a moment to the patient perspectives, because this is a devastating disease. Patients are overwhelmed. You know, I can't tell you how many patients walk into my office having read on the internet that they're going to die in 2.5 years. It's scary. So, it's important to really have good communication with the patients and at every visit discuss, you know, not just how they're doing with their test results, but how they're coping, where they are in terms of their quality-of-life and their treatment goals. And I know that this concept of shared decision-making, it's kind of a buzzword, it's kind of loud, but I think it's so important in this disease which has not just a high mortality, but many treatments, some of which are very complex and have a number of side effects associated with them. So, really critical to sit down and go through all of that with the patient. It's important that the patients have resources that, you know, if possible, I think many patients should be managed or comanaged in a PAH center. But there are also very active patient organization support groups that have resources for patients. And as much as I hate to say it, because patients come to us for hope and you know, I've been treating this disease for a long time and we're very aggressive with treatment. Sometimes we're not going to win it and the patient might not be a candidate for transplant, so it's often important to start broaching the concept of palliative care.

Palliative care, I think is in the best interest of some patients, and it provides some patients with this interdisciplinary medical care that might improve their quality of life, alleviate their symptoms and can be given concurrently with some of the other therapies that we use.

And as I said, shared decision-making, engaging the patients. Really talking about the medication's adherence, and you know, the patients helping to contribute to their care by self-monitoring is something that we need to do that every single visit.

I love this quote: Patient-centered care is providing care that is respectful of, and responsive to individual patient preferences, needs, and beliefs, and ensuring that these values guide all clinical decisions. So you know, I think we should all try to live by that every day as we treat PAH patients. And the share approach is really seeking the patient's participation, helping the patient explore and compare treatments, assessing the patient's values and preferences, reaching a shared decision with your patients. And then, evaluating how the patient is doing with that decision.

This is a list of the – or – a map of the comprehensive care centers. This is a certification process by the Pulmonary Hypertension

Association and of course, there are also support groups too. And there's a link there to see if there are support groups near where you practice for your patients.

So, this is the figure that I'll close with, it's again, from the ESC/ERS guidelines. I really like this figure because it puts things in perspective that worldwide PAH is common but as we've already talked about, there are five different types of PAH, and that Group 1 PAH, where so many of these therapies are available, it's actually pretty rare. The most common types of pulmonary hypertension we're all going to see every day is Group 2 pulmonary hypertension due to left-heart disease, and Group 3 pulmonary hypertension due to lung disease.

So, I think with that I will go on to the questions again. So, we'll see hopefully you've learned a little bit about. We'll see what the responses to those questions are. So, based on the 2022 ESC/ERS guidelines, a key tricuspid regurgitation velocity of greater than 3.5 is indicative of what: Low probability, intermediate probability or high probability of pulmonary hypertension? So, I'll let you vote.

OK, let's see. Yeah, so most people got that right. High probability for the TR velocity. So, greater than 3.4 is indicative of high probability. But of course, it's important to remember that we also want to put that in context with the other 2D findings and Doppler findings on exam.

The next question is, the individual that is newly diagnosed and a REVEAL score of 12, which puts them in a high-risk category, not vasoreactive, no comorbidities. What is the best treatment? Calcium channel blocker plus ERA, ERA with PDE5 inhibitor, ERA PDE5 inhibitor and parenteral prostacyclin, or monotherapy PDE5 inhibitor, or ERA?

OK, let's see what you thought was this one. Yeah. Most of the – the participants got that right. So, this is a high-risk person. They should have triple therapy that includes a parenteral prostacyclin, and that's in the ESC/ERS guidelines and in the last oral symposium. So, triple therapy with a parental prostacyclin [mic cut out].

And then, the last question in the Phase 3 STELLAR trial, which emerging therapy resulted in a greater improvement in exercise capacity compared to placebo for patients with PAH on once-daily background therapy? So, MK5475, erlotinib, seralutinib, or sotatercept? So, go ahead and vote.

Let's see the response. Yeah, that's great. Almost everyone got that right. So, sotatercept, which was the signaling inhibitor that was studied in the STELLAR trial hit the primary endpoint of exercise capacity based on 6-minute follow-up, and then any other secondary point.

So, it's time for the Q&A.

**Dr. Kesler:**
All right. Thank you, Dr. McLaughlin for an excellent session. We have a bit of time for Q&A. And so, we'll try to get to as many questions as we can. Dr. McLaughlin, our first question can you tell us a little bit about exercise PAH?

**Dr. McLaughlin:**
Yeah, I think it's a really great question and, you know, when you think about it, our patients complain most commonly of shortness of breath with exertion. But when we do that heart catheterization, they're lying there on a table not doing anything. Now, of course, many of them will have hemodynamics that are abnormal, but sometimes when a patient is really symptomatic, but their resting pressures are normal, we exercise them to see if they develop an elevation of their pulmonary artery pressures with exercise that might explain their dyspnea. So that is the purpose of doing an exercise right-heart cath.

Now, interestingly, the PA pressures may go up with exercise because the left-heart filling pressures go up. It could be that we're eliciting exercise induced diastolic dysfunction, but especially in patients that we, you know, we worry about pulmonary hypertension and they have a risk factor or they have a genetic defect that predisposes them, if we exercise them and their mean bone artery pressure goes up a lot and their wedge pressure doesn't, they worry that is really the early development of pulmonary hypertension. And that new definition in the ERS/ESC guidelines is the slope. We're measuring it by the slope of the increase of the mean pulmonary artery pressure divided by the cardiac output.

**Dr. Kesler:**
Perfect. Thank you so much.

Can you tell us a little bit about your experience converting someone from sildenafil to tadalafil or vice versa?

**Dr. McLaughlin:**
Yeah. So it's really interesting. Sildenafil in the clinical trial was studied at doses of 20, 40 and 80. They all improved 6-minute hall walk and there was not a dose response in the primary end point of hall walk, although there was a little bit more improvement in the

hemodynamics in the higher dose. But the FDA has approved the dose of 20 milligrams TID. In tadalafil in the studies, there was a dose response in terms of the exercise capacity and secondary endpoint of time to clinical worsening, so that is FDA approved in a dose of 40 milligrams a day.

So, usually when I switch back and forth, like I use the FDA approved doses. Some people use higher doses of sildenafil, you know, depending on whether or not insurance will pay for it.

**Dr. Kesler:**
Perfect. Thank you so much. When you're assessing PAH, do you use an RVSP of 35 millimeters of mercury or 40 millimeters of mercury on Echo to state that the RVSP is high and may suggest pulmonary hypertension?

**Dr. McLaughlin:**
Yeah. So I think this was really an emphasis point of the ERS/ESC guidelines and they wanted to get away from RVSP, because you know, that is also adding the right atrial pressure and there may be some variation in how people do that. And so, they went to velocities to the TR velocity. And so, 3.4 is what they say is the high-risk velocity. So, that's really what we should be focusing on rather than the RVSP, so many ECHO reports will get the velocity as well. So, 3.4 is the high response.

**Dr. Kesler:**
Perfect. Thank you. Can you tell us a little bit about troubleshooting patients in the hospital who may be suspected to be on too high or too much of a prostacyclin?

**Dr. McLaughlin:**
Yeah, sure. And it doesn't necessarily need to be just in the hospital. Sometimes we see patients in clinic, and we worry that they are on too high of a dose. You know, so a lot of it is the side effects, and it's really important when we titrate prostacyclin to try to balance the side effects of the prostacyclin with the symptoms of the disease. But side effects is one thing. You know, really when their skin is very flushed is another thing. But really how we tell for sure if someone's on too high of a dose is by a right-heart cath, and if their cardiac index is too high, if it's, you know, if it's above 4, they are on too much prostacyclin. So, I would say rely a little bit on symptoms, but it's really the heart cath that's going to tell you if you've got the right dosing.

**Dr. Kesler:**
Great. Thank you so much. And I think one last question for you. Can you tell us about your experience using anticoagulation for PAH, or do you still use anticoagulation for pH?

**Dr. McLaughlin:**
Yeah, this is a great question, too. Anticoagulation had been studying back in the day prior to many of the therapies that we have available, and in some observational studies it looked like patients were living longer and it kind of became standard-of-care, but without very good evidence. More recently, in registries in patients that are current-day on our background therapies, there's no ligit – there's not been any demonstration of a benefit – of a survival benefit. And even some of the groups, like patients with scleroderma had worse outcomes with anticoagulation. So, we do not use anticoagulation anymore in PAH unless they have another indication, they've had a DVT or something like that. So, we generally don't use it anymore.

**Dr. Kesler:**
Beautiful. Thank you so much.

Thank you again to all of our learners. It's been a pleasure having you this evening. Please be sure to go online to claim your credit for this session. You can find the link in the Resources tab along with the downloadable slide set.

Thank you so much and have a great evening.

**Dr. McLaughlin:**
Thank you.

**Announcer Close:**
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