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Conversations About PAH: Latest Developments and Key Insights for 2023 – Case Discussion

Announcer:
Welcome to CME on ReachMD. This activity titled Conversations about PAH: Latest Developments and Key Insights for 2023 Case Discussion is provided by AKH and supported by an independent medical education grant from Merck, Sharp and Dohme Corporation, a subsidiary of Merck & Company, Inc. This replay of a live broadcast focuses on key insights about pulmonary arterial hypertension, PAH.

Now, here's your moderator, Dr. Jennifer Caudle.

Dr. Caudle:
Pulmonary arterial hypertension, or PAH, is a chronic and progressive condition that affects the pulmonary vasculature resulting in elevated pulmonary vascular resistance, right ventricular dysfunction, and eventual right heart failure. It's essentially – it's essential to identify and manage PAH early to improve patient outcomes. Due to the inadequacies of current therapies, it's necessary to critically evaluate novel treatment pathways and new emerging therapeutic targets for PAH.

In this clinical discussion you'll hear from two leading experts who will discuss patient cases and discuss how you can optimize PAH treatment plans based on risk stratification and comorbidities, and integrate the evidence-based recommendations and treatments in your practice.

So, now, I'm your host, Dr. Jennifer Caudle. Thank you so much for being with us today and I would like to welcome Dr. McLaughlin and Dr. Channick to the program.

Welcome to the program doctors McLaughlin and Channick.

Dr. McLaughlin:
Dr. Caudle, thank you so much for having us.

Dr. Channick:
Pleasure to be here.

Dr. Caudle:
Well, it's wonderful to have you both. So, please note for those of you who are listening, our disclosures are available to you on the event page. Also, you will have the chance to claim credit by completing an evaluation after participating in the course, and finally, to submit questions during the presentation which we hope you will. Please type them into the chat control panel on the left throughout the program. We'll try to answer as many of your questions as we can during the time allotted.

So, we have a lot to discuss. Let's begin. Dr. Channick, I'd like to start with you. Can you briefly review PAH diagnosis and classification?

Dr. Channick:
Yeah, I'd be happy to. Maybe if we can start with the first slide. The good thing is that there is a very clear guidance in how we diagnose pulmonary hypertension and pulmonary arterial hypertension. In this slide, it's a nice sort of current, up-to-date description of what does

that workup involve. So, many times we're starting with echocardiography. It really is a good screening test for determining the likelihood that pulmonary hypertension is present or could be present. And I think one important point is that, you know, if we have a very high suspicion for hypertension, we're really stressing early referral to expert center where they have the expertise to perform a detailed workup. We then have other testing to look for why a patient has pulmonary hypertension. I think the other important concept here is that we think about things like left heart disease and lung disease, which really are the most common causes of pulmonary hypertension, first, before we really get into great detail of why a patient has, or could they have a rarer form of pulmonary arterial hypertension.

And if we could look at the next slide, it kind of breaks it down a little bit further where we're looking at the echo trying to assess how significant the pulmonary hypertension could be, do they have any obvious left heart disease. We're doing pretty routine testing looking for lung disease, sleep disorder, breathing. And then, if we look at the next slide, we really do stress the concept of excluding chronic thromboembolic disease, it's an important one because it's not always thought about. We've learned that if you don't think about chronic thromboembolic disease, you're going to miss the diagnosis. So, the VQ scan is really a critical part of that workup. And then, we really stress that we always need right heart catheterization to really confirm a diagnosis. Can't diagnose pulmonary hypertension simply with an echocardiogram. And the right heart cath serves many purposes looking for left heart disease, looking for vasoreactivity. And then there are a number of other caths that can be done to try to subgroup a patient who has pulmonary arterial hypertension.

And if we look at the next slide, I think we can see what really has existed for a few decades now as a clinical classification system, which I think still has, you know, utility where we can think of patients in one of 5 broad groups as to why they have pulmonary hypertension. Do they have pulmonary arterial hypertension or this pulmonary arteriopathy. Do they have PAH due to left heart disease; group 2, due to lung disease; group 3, due to chronic obstruction of the pulmonary artery – usually chronic thromboembolic disease but not always. Or do they have some multi-factorial pulmonary hypertension. For this classification system at the end of the day I think is still quite useful.

Dr. Caudle:
Excellent, and thank you so much for that. Dr. McLaughlin, what's the purpose of risk stratification in patients with PAH?

Dr. McLaughlin:
Dr. Caudle, risk stratification is so important in PAH and we've learned so much about risk stratification over the years. It's important to assess the severity of the disease and help us determine the risk of clinical worsening, or even mortality, and so, this really helps us tailor our treatment and monitor our patient over time. There are a number of well-validated objective risk stratification tools. The registry was based on a large – or the REVEAL risks score was based on a large US registry. The COMPERA and Swedish Pulmonary Arterial Hypertension Registry also developed risk scores mainly based on the risk stratification tools from the ERS/ESC guidelines and then the French Pulmonary Hypertension Network demonstrated the use of a number of factors and risk scores that include both invasive and non-invasive parameters. There is a tremendous amount of overlap in the data points in these different risk scores. There's some information about demographics in some of them, but functional status, labs, hemodynamics, for example, are important.

Traditionally, we have lumped patients into three different risk categories; low, intermediate, and high, and the intermediate risk group was very, very large and there have been some more recent attempts to delineate that group a little bit further. So, risk assessment is important at the time of diagnosis, and it helps us select the initial therapy for a patient, but then it's also important to reassess a patient longitudinally and, in fact, the risk assessment is really integral to the treatment algorithm. We do it every step along the way in order to further tailor our therapy.

Dr. Caudle:
Thank you for this. And, Dr. Channick, back to you. You know, what factors are typically included in risk stratification models for PAH?

Dr. Channick:
Yeah. Quite a few as it turns out. So, one of the really important concepts is that risk assessment, or risk stratification, is really a multimodal tool. No one parameter can tell you where a patient falls in the risk category, and I think cases that we'll show in a little bit will really exemplify that. So, if you look at this slide, it really shows you all the different parameters that we look at from, you know, symptoms, subjective things like, are the patient's symptoms progressing quickly, what is their functional class, do they actually have signs of heart failure, to more objective parameters like, I-O markers, NT-proBNP. We can do exercise casting 6-minute walk or CPET that are sort of fairly semi-objective. And then we look at right ventricular function with echocardiography and even invasive hemodynamics, and all of these parameters really go into risk assessment. So, it's a multimodal approach that's really critical.

Dr. Caudle:
And for those of you who are just joining us, this is ReachMD and I'm your host Dr. Jennifer Caudle. Joining me to talk about PAH are doctors McLaughlin and Dr. Channick. And I'd like to encourage our viewers to submit questions for them as well.

So, Dr. McLaughlin, let's come back to you. What are the limitations of current risk stratification models in PAH?

Dr. McLaughlin:
Yeah, so we've got a tremendous amount of data looking at how accurate some of these risk stratification models are in terms of predicting outcomes and, as Dr. Channick just outlined, it's a multimodality assessment. We look at exercise tolerance, biomarkers, some of them include hemodynamics as well. But, in reality, there are some limitations of these factors, both in terms of the actual measurements we're making, and in terms of the patient population. For example, the 6-minute hall walk, it's really based on absolute numbers, you know, and absolute hall walk of 440 is – or above that, is a good prognostic indicator. But I can tell you, 440 is not good enough for a 20-year-old, 6-foot man and, on the other hand, my 75-year-old, 5'1" lady with scleroderma is never going to walk 440 meters no matter how good her pulmonary hypertension medications are for her. So, that's a limitation of 6-minute hall walk. For example, functional class, you know, it's crude but it's very predictive. But there are other things that impact functional class. We have lots of patients with connective tissue disease that have musculoskeletal limitations and so, they may complain of a lot of limitations despite their pulmonary hypertension being well-controlled. So, overall, risk scores are really good, but they're not perfect and there are other factors that need to be considered.

Dr. Caudle:
That's a really good point. And Dr. Channick, how do current guidelines recommend risk stratification in patients with PAH?

Dr. Channick:
Yeah, so if we look at the next slide, and Dr. McLaughlin will go into this, I think, in more detail. I mean, the guidelines are very clear that risk stratification should be done both in baseline and as follow-up. And I think which tool you use for risk stratification, you know, I think the guidelines are pretty clear that there's not one that should always be used – that you should have a tool that you use, and you use it routinely and regularly. And this is sort of a global list of some of the parameters I kind of alluded to that go into risk stratification. But, you know, the risk stratification tools really have become critical for really informing therapy and changes in therapy using some of these various parameters that we maybe get into a little more detail.

Dr. Caudle:
Great. And, Dr. McLaughlin, what are the different risk categories used in PAH risk stratification?

Dr. McLaughlin:
Sure. I think this slide nicely highlights what we've learned about prognosis and risk assessments over the years and there's some very good data to support most of these measurements in terms of the risk being either high, which we believe is consistent with a great than 20% one-year mortality. So, that's a very high risk. And the factors that you low risk with less than a 5% one-year mortality. I think one of the problems that we've had is that intermediate risk group where the range of mortality is 5 to 20%. That's a pretty big range. And historically, about 70% of patients have fallen into that intermediate risk group. With some of the more recent data from COMPARA and then validated by the French registry, we now separate that intermediate risk group out into intermediate low and intermediate high, and they have very different Kaplan-Meier curves. So, they're very different populations. And, so, generally we do a risk assessment at baseline. The ERS/ESC guidelines still recommend using the 3 strata, this intermediate low and high as we see here at baseline, although I can argue that we should be thinking about intermediate low and intermediate high at baseline as well. But then, with the follow-up assessments, using the 4 strata that includes low, intermediate low, intermediate high, and high risk.

Dr. Caudle:
And Dr. Channick, back to you. Now what are the key components of the REVEAL 2.0 calculator?

Dr. Channick:
Yeah. So, the REVEAL 2.0 calculator, you know, is really a pretty powerful tool. We've alluded to some of the other risk assessment tools and Dr. McLaughlin sort of identified one of the limitations is that many patients fall under that intermediate risk category on follow-up and this 4-strata model attempts to correct that. One of the powerful things about the REVEAL, unlike the other models, is it gets you a number. It's almost a continuous variable and by doing so, your patients can, you know, go from a very low number, which is good, to a very high number, which is bad, and everything in between. It really can discriminate in a more powerful way prognosis in various categories, and it's been shown to do that and well-validated.

The other aspect of this, not to get into, like, great detail on all of it, is that, you know, it accounts for things like baseline stuff, like who is the patient, you know, what is there demographic. What kind of pulmonary hypertension do they have. Those kinds of parameters that have been shown to contribute to outcomes and to prognosis. And, so, if you look at these various parameters here, some of them are shared by the other tools, but there's certainly a lot more sort of granularity with vital signs, have they had a hospitalization recently, those are things that really, I think, increase the power of this tool.

And what I think, is that there's actually an app and at our institution we have it embedded into our electronic medical record that we do it on, sort of a regular basis.

Dr. Caudle:
Great. Dr. McLaughlin, what are some of the limitations of risk stratification?

Dr. McLaughlin:
Well, you know, Dr. Caudle, let me share a case with you to try to demonstrate one of the limitations, I think, that we have. And these are the type of patients that keep me up at night. Rich, I bet you have many patients like this, and we can probably talk about it. So, this is a young woman, 45-years-old. I've been seeing her for a long time, and she's been on triple therapy with intravenous epoprostenol, tadalafil and macitentan and she's sick, and she's still sick despite that. Her last heart cath was just this past November, at which time she had a mean pulmonary artery pressure of 81, a right atrial pressure of 7, a normal wedge pressure, cardiac index in the normal range. But look at that, her pulmonary vascular resistance was 16.2 Wood units. So, really sick, right? Like, those are advanced hemodynamics. But she's young and she functions really well, so, I actually saw her even more recently than January and these numbers are still the same. She's functional class 1, she does whatever she wants, her hall walk is 617 meters, so, well over that magic number of 440, and her BNP was 48, and when you do an objective risk score on her, she falls into the low-risk category by both the 4 strata and the REVEAL lite 2 method. So, you know, if you just look at that you say great, no problem, low risk. You know, we don't need to do anything different.

Rich, do you have patients like this?

Dr. Channick:
We do, we do indeed, and, you know, just like you said, Val, I mean, the right heart cath obviously shows some very, you know, high points of vascular resistance, standard cardiac index by least invasive hemodynamics and is reasonable and her right atrial pressure is low, but as you said, she's young and, you know, functional, but that doesn't tell the whole story.

Dr. McLaughlin:
Yeah, she compensates well. If we go into the next slide, I've just chosen two images from her echo and here's another, in my opinion, limitation of the risk stratification tools; it doesn't include cardiac imaging. And I imagine one of the reasons it doesn't include cardiac imaging is that we don't have great ways to objectively assess the right ventricle. There's variability in the availability of echo in the databases or, you know, qualitative versus quantitative interpretation. But, as you can see from this echo, her right ventricle is really big and really dysfunctional. So, for those of you who aren't familiar, this is basically the heart upside down so the top left is the right ventricle, which is bigger than the left ventricle and dysfunctional, and the bottom left is the right atrium, which is also enlarged.

And then, if we go to the next view, the other one that I've chosen is the parasternal short-axis view and, for me, this I think is probably the most important view. If you told me I could only have one picture on an echo, this is what I would want to tell how sick a patient is. It really tells you a lot about the interaction between the right and the left ventricle. And here, you can see that the left ventricle is small and underfilled, the septum is de-shaped - the left ventricle is not a donut or a bagel, it looks like a D, and that septum belongs to the right ventricle. So, I look at that and I worry about this patient. I don't care that her risk score is very low, I'm really concerned about her. So, I think this is a limitation. You know, these young people who function well despite having this disease and who can look low risk by scores, but I've just showed you hemodynamics and an echo that make me worry about this patient. So, the risk assessment is underestimating, in my opinion, how sick this patient is.

Dr. Caudle:
Those are really excellent points. Thank you, both of you, for commenting on that case. Very helpful. For our audience, I'd like to give you a quick reminder that we do encourage you to submit questions for the faculty. To submit questions during this presentation please just type them into the chat control panel on the lefthand side throughout the program. We're going to try to answer as many questions as we can during our time allotted.

So, you know, similarly, Dr. McLaughlin, are there times when objective risk stratification tools overestimate risk? Is it sometimes okay if one doesn't achieve low-risk status?

Dr. McLaughlin:
Yeah, and that's a great question that I think is even more common than the case I showed you. So, here's another one of my patients. She's 75. I've known her for over a decade. She has scleroderma and our scleroderma program is very aggressive about screening patients for pulmonary hypertension. So, I met her in 2012 and we did a right heart cath because she screened positive and you can see her hemodynamics there; a mean pulmonary artery pressure of 33, a wedge pressure of 11, a normal cardiac index, her pulmonary vascular resistance was 3.2 Wood units. So, this is great. This is what we want to do with the screening program is try to get patients

early in the course of the disease. So, catching patients with a pulmonary vascular resistance of 3.2, I think, is really good. If we did that more often, I'm sure we'd be much more successful with our outcomes. So, based on that pulmonary vascular resistance, she was treated with PDE5 monotherapy. We repeated a right heart cath, I guess it was most recently done in 2019. Her PVR was 2.8, so, I think by all accounts that means that we're doing a pretty good job with her pulmonary hypertension therapy. But she's older, she has scleroderma, she has comorbidities that can impact her functional capacity. So, when you talk to her, she's a functional class 3. You know, she has limitations, she gets short of breath with stairs. When you walk her, she's well below our goal. Her walk is 244 and her BNP is 128 and again, she's older. It could be from the right heart, but she also has some risk factors for diastolic heart failure, so maybe it's from the left heart as well.

So, when you do objective risk scores on her, she falls into the intermediate high-risk category by the 4 strata method and intermediate by REVEAL lite 2. So, Rich, she's not at low risk. Should we be adding therapy to this woman?

Dr. Channick:
Yeah, I mean, this has been – this is the issue. I mean, no, certainly, I mean, but I think that sort of as the last case showed, I mean, risk strata, right, it's a population-based estimate, and I think can't necessarily apply to every individual patient. I think this patient is potentially a perfect example of that. She's, you know – there are other things that could be limiting her symptoms and her walk distance, her age, her underlying disease, and that's not going to be accounted for necessarily in this risk strata. So, I'd like to see what, you know, her right ventricle looks like clearly before I'd make any decision about additional therapy.

Dr. McLaughlin:
Right, so, let me show you what her right ventricle looks like. If we could go to the next slide. So, this is her echo. So, again, the right ventricle is on the top left. It is smaller than the left ventricle, it's squeezing well. The left ventricular function is normal. Her right atrium actually looks pretty normal, bottom left, but her left atrium on the bottom right looks a little big and it looks like there's some bowing of the intra-atrial septum from the left to the right. Maybe her left ventricle is a little thick, too. Maybe she's a 75-year-old woman who has some diastolic dysfunction contributing to both her symptoms, to her hall walk, to her elevated BNP, and on the short axis view on the next slide, you can see that the left ventricle is that perfect bagel, that perfect donut. The septum belongs to the left ventricle. The right ventricle is a small, just it lips around – I'm sorry, the right ventricle is a small ellipse around the left ventricle. It's not pressure overloaded, it's not volume overloaded. So, this is a great example of, gosh, I feel really comfortable that this patient's pulmonary hypertension is well-controlled. That right ventricle looks normal. A cath just a few years ago showed a normal, or a near-normal pulmonary vascular resistance and this is the sort of patient where I say, even though she's not meeting low-risk criteria, there are other factors that are contributing to that risk status. The right ventricle is in good shape. I do not believe that the pulmonary hypertension is the driving factor and I do not believe that we need to escalate therapy. And, so, I think it's really important to use risk stratification tools, but to also realize that there are other factors that should be taken into consideration, including the age, the comorbidities, and what that right ventricle looks like.

Dr. Channick:
This, in fact, and just to add to that, you know, potentially could make it worse by adding additional therapy.

Dr. McLaughlin:
Yeah, absolutely.

Dr. Caudle:
Well, thank you both for commenting on that case. Again, very interesting. I certainly found it very interesting. I know our viewers are as well. Dr. Channick, how frequently should risk stratification be performed in PAH patients?

Dr. Channick:
Yeah. So, there's some good guidance on that. I think that we, you know, do it regularly and if you read the guidelines, and so we want to do it at baseline, and you want to do it with regular follow-up. Usually, you know, more frequently early on in the course of the disease and then less frequently later. So, maybe the initial, follow-up risk assessment at 3 to 4 months and that's going to tie into, you know, making therapeutic decisions about changing treatment. You don't want to wait too long to make those treatment decisions. And then, you know, it may go to every 6 months and occasionally once a year if a patient's doing really well. So, I think we can stretch it out as you get further along in the course of treatment and once we made those changes in treatment or treatment decisions. But the key message is, you need to do it at regular intervals.

Dr. Caudle:
Great. And Dr. McLaughlin, back to you, you know, what's the significance of a high-risk classification in PAH patients?

Dr. McLaughlin:

Yeah. It's a great question and I think we really need to focus on this because high-risk, as I said, in that table, that's a greater than 20% 1-year mortality rate. That's really high. And, even though we've made advances in medications, and we have overall therapies, patients who are at high risk often need more substantial therapy that includes parenteral prostacyclin therapy. And, whether they're at high risk because they're in florid right heart failure or because their cardiac index is 1.7, we really need to aggressively treat those patients. They're a small proportion of the patients, I would say less than 10% of the new patients that I see, but that is really an urgent situation that we need to be aggressive with.

Dr. Caudle:
That's great. And, staying with you, Dr. McLaughlin, what are some of the key conclusions we can make from the patient cases you presented?

Dr. McLaughlin:
Yeah. So, I think, just discussing risk assessment in and of itself, we have a lot of wonderful objective tools to assess risk. And risk assessment should be done pretty much with every clinical encounter. In fact, we do the things you need to get a REVEAL risk score, or on a 4 strata, every single clinic visit. Its functional class, it's hall walk, it's biomarkers, it's vital signs, it's kidney function. We do that every time we see a patient. And, so, we should be doing an objective assessment and documenting it at every visit. Just like Rich, we have embedded in our electronic medical record both the REVEAL 2.0 lite and the 4 strata. So, we do that. And that really serves as our goal, our north star, as we treat patients. We want to try to drive them to low-risk because we know the outcomes are better if they are at low-risk status. However, as we exemplified with the patient cases, there's much more to risk assessments than that, and it is, as Dr. Channick outlined, a multimodality process. So, imaging the right ventricle I think is a really important part of it and it can complement those objective risk assessment tools. So, the patient who's not low-risk but has a normal-looking right ventricle, you have to think about the other things that are contributing to their functional capacity that make them not low-risk.

As we meet new patients, most of the time we start those who are at low and intermediate risk on dual oral therapy. Those patients, that small proportion of patients that are high-risk, need more aggressive therapy with parenteral prostacyclins. But that's just the first step. We need to reassess the patients regularly.

Dr. Caudle:
Alright, thank you. And Dr. Channick, what are some of your key conclusions from the patient cases?

Dr. Channick:
Yeah, I think, Val stated perfectly. I think that, you know, obviously the whole role of risk assessment and looking at these cases is in making treatment decisions, whether to add treatment or the second case, not to add treatment. And I think that we've kind of summarized that in our discussion. I mean, this is the – this slide shows you sort of, a generally accepted initial approach to treatment. There is probably still a role for vasoreactivity testing. We don't talk about that much because it's very, very rare that a patient is started on a calcium channel blocker, so that's almost an anomaly when that happens in a very rare patient with idiopathic PAH, typically a young patient that they're highly vasoreactive. The vast majority, you know, we're doing this risk assessment similar to how we've outlined. This lower intermediate risk starting on the dual therapy, dual oral therapy, but then keeping in mind that in the high-risk patient, parenteral prostacyclin therapy in addition to the oral therapy. And that's kind of a newer call-out, is that even the patient you start parenteral therapy for high-risk should also be started on the oral therapies that work through different mechanisms that we've outlined.

Dr. Caudle:
Okay, great. Now that's very helpful. And, Dr. McLaughlin, you know, back to you. Some key conclusions from the patient cases. Any further thoughts about that?

Dr. McLaughlin:
Yeah. I guess the one thing I would just leave you with is, even though we've come so far, even though we have many therapies, and that first case was on three therapies and still had an ugly-looking right heart, so, even though we have those therapies, we still need to do more. There are many other dysfunctional pathways in the pathogenesis of PAH besides just those three pathways that we currently target and so, this is an area of really active research right now, looking at medications that effect other pathways that may do more than just vasodilatation that may really remodel the pulmonary vasculature and potentially cause reverse remodeling of this disease, so hopefully we'll have more options in the not-to-distant future.

Dr. Caudle:
No, understood. You know, we're coming to the conclusion of our program, actually we've got a few other things to do, we've got question and answers, but I actually do have a question as a family doctor, you know, it's always a delight talking to both of you about PAH. You know, for any of our listeners out there who might be in a primary care specialty, or field rather, do you have any tips or

pearls for those of us when it comes to detecting patients that need referral, screening patients? You know, Dr. McLaughlin, you mentioned one of your patients had scleroderma. Are there certain conditions we need to have a higher alert for? Just, you know, this is a little off the record, but I would love any just sort of commentary that you have about that.

Dr. McLaughlin:
Yeah. Maybe I'll start with the tips about the workup and then maybe Rich will comment on the populations to screen. So, I can imagine how difficult it is as a family physician, or primary care physician, you probably have people complaining to you about shortness of breath day in and day out. Right? That's the most common symptom of pulmonary hypertension and most of the time it's not going to be pulmonary hypertension. So, what I think is important is that you do the work up, you look for the common things that you think it may be, but when you don't find that diagnosis, when it's not asthma, or when the stress test is negative, have a low threshold to go to an echo because the echo is really that modality that really raises the suspicion of pulmonary hypertension. And when you look at the echo, it's important to look not only at the estimated RVSP, but at other findings on the echo. The size and function of the right ventricle, if it's enlarged and dysfunctional, we're a lot more worried about that patient. Or, learning something about the left heart. If there's LVH and grade-3 diastolic dysfunction, it's more likely HFpEF. So, I would just encourage the use of echo early on as you assess some of these patients.

Dr. Caudle:
I love that. Thank you. And Dr. Channick, any advice for myself and my colleagues.

Dr. Channick:
Yeah. I mean, I think it's, you know, medicine starts with the history, right? You know, you get – and if you go back and look at these patients that have already been diagnosed, if you go back in the history, you can see warning signs or things that, you know, would've raised your suspicion. I mean, there's clearly identified risk factors. Unfortunately, illicit drug use is one of the big ones that's really emerged as a very strong risk factor for pulmonary arterial hypertension, specifically stimulant drugs, like methamphetamine and cocaine, which you know, in certain parts of the country, almost probably most parts of the country now, are unfortunately, are very rampant. So, really looking at drug history, a detailed drug history, or even things like chemotherapeutic agents that patients are on, kinase inhibitors like dasatinib, that are highly associated. So, getting a good medication and illicit drug history. And then, looking for kinds of connective tissue disease. I, as I'm sure Val has, diagnosed scleroderma in patients, you know, as a non-rheumatologist, you come in and you look at their finger. So, it starts with the basics.

Dr. Caudle:
Yeah. No, that's excellent. And thank you for those pearls. So, lets move on to the question-and-answer section. We have a number of questions that we've been asked, which I'm excited to post to you both, or each of you separately. The first question, and I'll let you decide who wants to take this, the first question is can you discuss any new or emerging therapeutic targets that show potential for the treatment of PAH? Who would like this one?

Dr. McLaughlin:
Yeah. So, I think, we're so excited about some of our clinical trials. So, probably the nearest thing is this agent called sotatercept, which is an activin trap. So, this works on the BMP pathway. There's dysfunction in the BMPR-II receptor in patients with pulmonary hypertension, and down-regulation of that and up-regulation of activin leads to cellular growth and reduction in apoptosis. And so, this agent traps that activin to kind of rebalance the pro-proliferative and the anti-proliferative effect on that pathway. This agent was studied in a phase 2 trial that looked at pulmonary vascular resistance and there was a statistically significant reduction in pulmonary vascular resistance in the phase 2 trial, which then led to the phase 3 trial, which was actually published in the *New England Journal of Medicine* just this past March. The primary endpoint of that trial was improvement in 6-minute hall walk, which is a very common primary endpoint in pulmonary hypertension, a very robust improvement in 6-minute hall walk in a patient population with pulmonary arterial hypertension that was treated with all of the medications that we have. Two thirds of them were on triple therapy, many of them were on parenteral prostacyclin. So, a very prevalent and pretreated population and yet still this very marked improvement in the 6-minute hall walk. And there were also improvements of 8 of 9 secondary endpoints. So, really consistent treatment effect over everything that was measured, including time to clinical worsening, including hemodynamics, including NT-proBNP, and even some quality-of-life measures, functional class. So, a really impressive clinical trial. So, that agent is undergoing the process of evaluation by the regulatory authorities then it may be approved as soon as early next year.

Dr. Caudle:
Excellent. We do have another question here. What challenges or barriers exist in implementing evidence-based care for patients with PAH? Who would like to take this one?

Dr. Channick:

I can take that. I think that, you know, we're going to break down the barriers, and maybe we've done a little of that today. The first thing is to, you know, really know the evidence and know what it shows. Well, you know, there's practicalities. I work in a very large pulmonary center with Dr. McLaughlin and even things like getting drugs authorized, I mean, these are expensive medications but we're using them I combination. So, you know, that authorization for the tests and then just getting patients to follow-up and understanding and having the infrastructure. So, those are some of the challenges, but we, you know, we look at it as a team approach, we use multiple specialists that help us, we have nursing support and others to try to really allow us to implement evidence-based medicine.

Dr. McLaughlin:
If I may just add one thing to that. I think it's really important for the community to understand the difference between pulmonary hypertension and pulmonary arterial hypertension and most of what Rich and I have talked about today is evidence around that group 1 pulmonary arterial hypertension. Rich reviewed the classifications earlier today and most of what we discussed, and certainly the drugs that we talk about, have been primarily studied in that group 1 PAH population. And while Rich was focusing on using the evidence-base in that population, I just want to also mention that that evidence doesn't really apply to some of the other types of pulmonary hypertension, and we can also do harm that way. Sometimes we see patients – or I see, I assume Rich does, too – patients who have high RVSPs on echo but have, you know, 5 risk factors for diastolic heart failure and have a big left atrium and someone wants to treat them with these drugs because they're short of breath. That's not the population that these therapies were studied in, so, I think we need to look at evidence-base from both sides.

Dr. Caudle:
That's a great point. Yeah. Thank you for that. Next question is, are there any specific risk stratification models that are recommended by leading professional organizations for PAH?

Dr. McLaughlin:
So, I think the key is to use some sort of risk stratification tool, whether it is the REVEAL lite 2 or the 4 strata method. The current ERS/ESC guidelines, which again are European based, use the COMPARA in their algorithm, but I think REVEAL lite 2 is fine as well. We do both. Sometimes they don't exactly align. But I think the message is to use a tool and don't just eyeball the patient, we're wrong when we eyeball the patient.

Dr. Caudle:
That's excellent. Thank you. Fourth question we have is how frequently should risk stratification be performed in PAH patients and what are the reasons for regular reassessment?

Dr. Channick:
You know, we talked about this a little bit and, you know, it's somewhat variable, but certainly you want to do it more frequently early in the course of the disease and treatment and then we can stretch it out when patients are doing well. Again, the purpose of risk assessment fundamentally is to determine if therapeutic changes or additions should be made and we like to make that fairly early on, not to get into too much detail. But there's pretty good data that the earlier you make these treatment changes, the better outcome you get and that probably makes sense, right? It's hit the disease hard early on and they do better. And so that's that 3-month after the initial treatment regimen is really critical in our opinion to reassess.

Dr. Caudle:
Great. Thank you. And our fifth question we have today is how do comorbidities impact risk stratification in patients with PAH and how are they incorporated into the risk assessment process?

Dr. McLaughlin:
Yeah. That's a great question. That's what I was trying to point out with the second case, and you know, a lot of the patients that we are referred now do have comorbidities, they do have hypertension or obesity or arthritis, and these can effect some of those factors that go into the risk stratification tools. The functional class and the hall walk, for example. And so, we need to take that into account and that's why sometimes we need complementary information like looking at the right ventricle from the echo. These are really not accounted for in any of the risk stratification tools at all, so we really need to look holistically at not just the risk stratification tools but also the patient and those comorbidities. And then some of the supplementary data that we get from the echo or from the right heart catheterization.

Dr. Caudle:
Okay. Excellent. That's wonderful. This has been such an enlightening program. I really cannot thank you enough. It's such a great way to round out our discussion on PAH, all of the commentary that you both have provided. I'd like to thank our colleagues today, Dr. Channick and Dr. McLaughlin. Thank you so much for really helping us better understand this topic. It was great speaking with you today.

Dr. McLaughlin:
Yeah. Well, thank you for having us, Dr. Caudle.

Dr. Channick:
It was a pleasure.

Dr. Caudle:
And for those of you who are listening to this course, thank you so much for joining us. Please proceed to claim your credit by completing the evaluation through ReachMD. Also, through ReachMD, you can get a PDF of the slides including explanations to the pre and post test questions.

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