Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/new-and-emerging-pah-therapies-and-approaches-a-mixture-of-hope-and-complexity/36095/

Released: 07/03/2025
Valid until: 07/03/2026
Time needed to complete: 60 Minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

New and Emerging PAH Therapies and Approaches: A Mixture of Hope and Complexity

Announcer:
Welcome to CME on ReachMD. This activity, titled New and Emerging PAH Therapies and Approaches: A Mixture of Hope and Complexity" is provided by Total CME, LLC and is supported by Actelion Pharmaceuticals US, Inc., a Janssen Pharmaceutical Company of Johnson & Johnson.

This replay of a live broadcast discusses new and emerging therapies for PAH. Find out why making the right diagnosis is key when determining your treatment approach.

Dr. McLaughlin:
Today we're discussing new and emerging PAH therapies and approaches. But before we talk about treatment for our patients with PAH, it's imperative that we make the correct diagnosis.

Join us as we discuss comorbidities, getting the right diagnosis, and who should and who should not be treated.

This is CME on ReachMD and I'm Dr. Vallerie McLaughlin.

Dr. Preston:
And I'm Dr. Ioana Preston.

Dr. Chin:
And I'm Dr. Kelly Chin.

Dr. McLaughlin:
Great. So we have a lot to discuss today and I'm going to kick things off by reviewing some of the history that was put into the ESC/ERS guidelines. As you know, this was published in 2022, and it's great evidence-based information. It's really a wonderful document. But they did something a little different with the treatment algorithm for the first time, and that is they pulled off to the right conversation about patients with comorbidities and how perhaps they should be treated a little bit more gingerly. They said patients with comorbidities should maybe get up-front single therapy as opposed to up-front double combination therapy, which is recommended for the patients with the more classic IPAH, or Group 1 PAH.

And that generated a lot of conversation. I personally think they didn't give a lot of guidance as to what's a comorbidity and how to put that in perspective with the severity of the pulmonary hypertension. So it's something that we talked a lot about as we moved into the 7th World Symposium on pulmonary hypertension and in that task force there was a great deal of conversation about that.

Now, Kelly, Dr. Chin, you were the lead. You actually did a yeoman's work on that chapter on creating the treatment algorithm and you and I were in the room. We had lots of discussion about the comorbidities part of it, in particular.

So maybe you can give us some of your thoughts on how the task force approached that, what they thought with regard to patients with comorbidities in the setting of pulmonary arterial hypertension, and are there some patients with Group 1 PAH who should be treated with monotherapy?

Dr. Chin:
So the comorbidities topic is definitely one that was of great interest, not just in our task force but I think in the World Symposium in general. And I think it was actually really helpful that the 2022 European guidelines called it out with such prominence, because it really got us all talking. Not just about how to treat these patients, but what do we mean by comorbidities, and how do we make sure that we're making the right diagnosis in our patient?

So when we started this conversation, some concerns that we had with creating a completely separate algorithm for those with comorbidities was that the group really isn't a homogeneous group.

The other concern that we had is that the clinical trial evidence base to support a separate algorithm is also more limited. But coming back to the group not being homogeneous idea, I think we're increasingly recognizing in cohort studies as we look in those today versus for many years ago, that some individuals with Group 1 PAH do have comorbidities and are relatively straightforward from a diagnostic standpoint. That means that they, although having a comorbidity, when you look at their heart catheterization and their echocardiogram and their overall clinical history, these patients do have fairly clear-cut Group 1 PAH. But in contrast, there's another extreme where the overall clinical picture is much more suspicious, actually, for Group 2 PAH, despite a catheterization that technically meets criteria for precapillary PAH. And so within the second group, I think you can probably even further subdivide it into patients who probably do have Group 1 PAH but are very complicated and have a lot of comorbidities. And then another group of patients who in reality may have an occult Group 2 PAH and we hadn't realized that this was as common in the past.

So I think the recommendation that we made with our task force was, overall, we have one guideline treatment-based recommendation for patients with or without comorbidities who phenotypically look like a Group 1 PAH patient who is enrolled in clinical trials and that we would focus on that patient group. In contrast, for patients where we are more suspicious of possible occult Group 2 PAH, and this might be things like a dilated left atrium or Grade 2 or higher diastolic dysfunction on ECHO or even a relatively higher wedge pressure that's still equal-to or below 15, that for these patients, we need to be much more careful and may need to look for occult left heart disease as the cause of their PAH.

Dr. McLaughlin:
Yeah, I think that was a great summary, Kelly. Like, really getting the diagnosis correct, knowing what you're dealing with. And you're referring to Group 2 PAH a lot because, frankly, it's so prevalent. We see a lot of it and there is a tremendous amount of overlap and a lot of thought that needs to be given into making the correct diagnosis. Does the patient need a fluid challenge? But there might also be overlap between other groups as well. And in fact, sometimes there's overlap between Group 1 and Group 3, especially in patients with scleroderma, for example.

So, Dr. Preston, maybe you want to elaborate on this, the differentiation of Group 1 from Group 3?

Dr. Preston:
Yes, Val. And like in Group 1/Group 2 conundrum, the patients may present with some features of lung disease, such as interstitial lung disease or chronic obstructive lung disease, and pulmonary hypertension. So how can we differentiate between Group 1 PAH with some comorbidity that's a pulmonary comorbidity versus overt underlying lung disease with pulmonary hypertension arising secondary to the lung abnormalities. And in some patients it's easy, and those are the patients who have significant hemodynamic impairment but mild lung impairment, mild interstitial lung disease only in the bases that we've seen many scleroderma patients with little or no restrictive lung disease on spirometry. Or patients with asthma with really normal spirometry at baseline but significant pulmonary hemodynamic impairment versus patients who have significant lung disease, severe interstitial lung disease with severe restriction or widespread emphysema on the CT scan and some element of pulmonary hypertension that is sometimes mild to moderate.

So that's the balance between how much hemodynamic impairment from vascular disease versus interstitial or obstructive lung disease is. It's sometimes difficult to ascertain, so it may be a continuum. However, I think the pathology, while it has some overlapping features of remodeling, there are some specific histological features that we see in Group 3 PAH with impaired diffusion capacity due to thickened interstitium in ILD or destruction, severe destruction of pulmonary vasculature in emphysema that we really need to understand what is the driving of the pulmonary vascular abnormalities? The primary vasculopathy, like in Group 1 with some lung comorbidity, or is it significant lung impairment and the pulmonary vascular disease is secondary?

Dr. McLaughlin:
Yeah, I think that was a great summary, and there was this one beautiful picture from a review article that we recently wrote that tries to balance that. I think you always have to take into context the severity of the underlying comorbidities, either the lung or heart disease, but also then put that into perspective with the severity of the PAH, how advanced the hemodynamics are, how much the right ventricle is affected. And I think it's not a one-size-fits-all. It's that whole zone of uncertainty of the wedge pressure that we discussed a lot that

needs to put a number of different characteristics into perspective.

So let's move on to risk assessment because the whole treatment algorithm is really predicated on assessing the risk both at baseline and then at follow-up. So maybe, Dr. Chin, do you want to tell us a little bit about some of the objective tools that we have to assess risk?

Dr. Chin:
Absolutely. So risk assessment in pulmonary hypertension typically consists of, during follow-up visits, assessing functional class, 6-minute walk distance, and, from the lab, BNP or NT-proBNP. And then, periodically, at most centers usually, RV imaging with echocardiography and right heart catheterization. These tests, along with others, are commonly combined together into risk calculators, and the 2 main groups of risk calculators in current use are the REVEAL-based calculators and then some from the ESC/ERS guidelines.

The US-based registry calculators include currently 2 different versions that are in use. There is a longer version that is REVEAL 2.0 and a shorter version known as REVEAL Lite. And in these calculators, points are assigned for each measure and then this is added together to get the REVEAL risk score which is used to determine whether a patient is at low risk, intermediate risk, or high risk of mortality at 1 year and other complications and is also used in the treatment algorithm.

The other commonly used risk calculator was derived from the tables in the ESC/ERS guidelines and also divides patients into low, intermediate, and high risk. There is a longer version that includes more echocardiography measures and other RV imaging from MRI and hemodynamics. And for each measurement, there's a low risk, intermediate risk, and high risk, and the overall score is basically based on the average of these.

So both of these types of calculators discriminate well between risk groups, but one issue is that the intermediate risk group, at follow-up in particular, ends up both being quite large and with differences in prognosis for those who are towards the lower end of the intermediate risk group and towards the higher end. And so the solution to this in the most recent guidelines was to further divide the intermediate risk group into an intermediate-low and intermediate-high risk group. And this is based only on functional class, 6-minute walk distance, and NT-proBNP, which do turn out to be the measures that are most predictive across all of these risk calculators.

So while there's some debate as to the best calculator, they actually both perform quite well and the key to putting it into practice, I think, is using these serially so that you can watch how this develops over time. Is your patient improving or worsening? And then applying this in a timely way to the treatment algorithm.

Dr. McLaughlin:
Yeah, that was a wonderful summary, Kelly. Thank you so much. And so you alluded to it: At baseline it's really are you high risk, are you not high risk? And that's really the big decision. But then in follow-up, one of the newer things is that we've split that intermediate-risk group into intermediate-low and intermediate-high, which I think is super important. The intermediate-risk group is the biggest group. If 70% of the patients are in one group, it's not really that helpful. So splitting it into intermediate-low and intermediate-high, I think, is really helpful as we talk to patients.

So, Dr. Preston, maybe with that background, you can discuss a little bit about how that newer concept was applied into the 7th World Symposium treatment algorithm.

Dr. Preston:
Yes, absolutely, Val. I think at follow-up it is as important as a diagnosis but maybe more so to evaluate a patient and the response to therapy. Our goal is to bring all patients to low-risk category and also, additionally, to look at the right ventricular function and improve it as best as we can towards normal RV function. So those are the goals clinically. But as you said, the majority of patients, unfortunately, do not reach this low score. So because the intermediate risk is a very gray area and it can spread towards the low risk all the way towards the high risk, the new 4-strata subdivided the intermediate risk into low-intermediate and high-intermediate. And this was applied into the recommended algorithm for follow-up treatment for treatment of patients with pulmonary hypertension in the sense that in the low-risk category there are a couple of options that do not include parenteral prostacyclins unnecessarily.

Whereas in the intermediate-high risk the treatment is geared towards how patients in high risk are treated with the recommendation to treat with parenteral prostacyclins and/or activin-signaling inhibitor. So a little bit more aggressive as if they were high risk.

Dr. McLaughlin:
Yeah, Ioana, that's a great summary. And I think that really makes it much easier to talk to a patient in clinic, right? Because intermediate is such a big, big range, just like Functional Class III is such a big range. And so if you're on the lower end of intermediate, it's a lot easier to talk about a non-parenteral prostacyclin, whereas if they're on the higher end, they're more orange, they're close to

red, we can get a little bit more aggressive. So I have found it very helpful as we talk to patients in clinic.

Kelly, do you have any comment you want to add to that concept?

Dr. Chin:
I think the one thing I would add is that probably the biggest change in the last 5 years is that we have moved our main point of reassessment after initial therapy from close to 1 year all the way up to 3 to 6 months. Because I think most of the benefits that you get from your initial therapy will be evident by that time, and we're just also recognizing how important it is to, in a timely way, escalate therapy when it is needed.

Dr. McLaughlin:
Yeah, I think that's a great point.

Now, we talk about these risk scores as if they're the holy grail but, of course, we know there are many, many issues that we need to consider as we talk about treatment choice. And you have alluded to them earlier, I think, Kelly, that how ECHOs are repeated and hemodynamics are repeated. And so I think that information can really complement an objective risk score.

So, Ioana, tell me a little bit about how you approach that in practice?

Dr. Preston:
Yes. We have to recognize that risk scores are very helpful. However, they do have their own limitations. The first, and I think the most important limitation, is the lack of RV assessment with some function on imaging that we need to complement with serial echos, sometimes with repeat right heart catheterization, as you said. But also taking into account the patient's wishes and their goals of what they should achieve, what they want to achieve from the treatment, the side effect profile, especially in certain patients. Some patients are more prone to develop sudden side effects versus others, so we have to put that into context.

And lastly, comorbidities. And I think the current algorithm recommendations removed the comorbidities arm from the treatment, but not to ignore them, but to make sure that we make the right diagnosis and offer the right treatment to the patients. But at the same time, we do have to take care of comorbidities and work with other healthcare providers of other specialties to treat those comorbid conditions that may contribute to the quality of life and symptoms of our patients.

Dr. McLaughlin:
Yeah, I think that was a wonderful summary. I guess I would just also add the whole concept of the risk score and there's potential impact of comorbidities on the risk score. I think we've all seen patients who, because of their comorbidities or if they're deconditioned, they're always going to be Functional Class III. Their hall walks are never going to be where we want them, but their RVs look pristine on echo, and so they're not meeting a low risk criteria but it's probably not because of the PAH. So I think it's important to consider all of those factors as we make some treatment decisions.

And we've all talked about the other end of the spectrum as well. That younger patient without comorbidities who's in great shape who is Functional Class I or II, who walks 700 meters, but their RV is big and dysfunctional. And I'm not happy with a low-risk score in that patient either. So I think there's a lot to balance here.

And then, Kelly, I'd actually like you to comment on one thing that I remember you talking about at the 7th World Symposium, and that is the concept of reassessing. Maybe someone does have a comorbidity but significant pulmonary hypertension, and you give them benefit of doubt, you treat them, and they don't improve. How do you approach reassessment of that patient?

Dr. Chin:
Yeah. I mean, I think sometimes the question is, we were right to begin with, but we have a secondary problem like anemia or some other condition, and thyroid problems are very common. But sometimes we were wrong in the first place and after starting an initial PAH therapy and I'm seeing the patient back and they're having all kinds of trouble with volume and they don't feel better and nothing seems to be going right. And we're, in general, a pretty strong believer in doing a repeat heart catheterization during that first follow-up, not in 100%, but in most of our patients. That is definitely a patient I would do that in because I'm looking to see what has the wedge done now over time and following PAH therapy and that type of thing.

Dr. McLaughlin:
Right, like maybe did you elicit occult diastolic heart failure with treating their PAH so aggressively, and maybe that's not the right thing for that patient.

Dr. Chin:
Yes, absolutely.

Dr. McLaughlin:
So this is great background. Getting the diagnosis right, assessing risk.

Let's move on to treatments. And it's been a really exciting past year or so in treatment. We have newer agents such as sotatercept. We have a combination tablet now that has tadalafil and macitentan, which is something we commonly use up front in combination for some of our newly diagnosed patients.

So let's talk specifically about that combination tablet, which was approved in March of 2024 and contains 10 mg of macitentan and either 20 or 40 mg of tadalafil.

Ioana, to tell me about how you talk about this, how you use it in your clinical practice.

Dr. Preston:
So, Val, we know that our PAH patients are, on average, on anywhere from 5 to 9 prescription medications. So adherence, compliance, tolerability, and copayments are all very important factors in treatment of our patients. So very recently, the combination of macitentan and tadalafil in 1 pill incorporated, basically, 3 pills: 1 macitentan and 2 tadalafil pills. And it reduces the pill burden for our patients who take them every day. It also may reduce their copayment, which sometimes is very burdensome for our patients. And it alleviates and it improves quality of life by taking less pills. So while we know exactly how the 2 pills work and we've been using them together for quite a few years, now that's a very more convenient way for our patients.

Dr. McLaughlin:
So let me ask you, and Dr. Chin please feel free to chime in, about how you've been using the combination pill. So certainly, as I have patients who already on both, I offer it to them. But on new patients, sometimes I like to know what's causing side effects, and I start one and then start the other and offer the combination if they tolerate both.

So, Dr. Chin, you probably have more experience than anyone with this because of your role in the A-DUE study, so do you want to tell us a little bit about that study and how you use this in clinical practice?

Dr. Chin:
Yeah. Let me start with A-DUE. So in this study, patients who were either treatment naïve or on background monotherapy with either a PDE5 inhibitor or an ERA, these patients were randomized to either the combination pill, with both macitentan and tadalafil, or to go to monotherapy. And if they were treatment naïve, they could be randomized to either. If they started out on an ERA, they didn't cross over to tadalafil, so that's why you see the 2 separate groups here. So the ERA patients would be randomized to either combination therapy or to macitentan, and then the same thing for the PDE5 inhibitors with tadalafil.

Patients underwent a right heart catheterization at baseline and again at 16 weeks. And then what we're looking at here is the change from baseline in PVR, basically, as a percentage. It's the geometric mean, is what's shown. And you can see there was a much larger improvement with the combination of macitentan and tadalafil versus either one alone. Keeping in mind that about half of the patients were coming from monotherapy and half were treatment naïve, and we see a little bit larger improvement with the treatment-naïve patients. But overall, still, I think fairly impressive results.

The other thing that was done with this study is there was a qualitative study that asked patients what they thought of the combination and asked physicians what they thought. And I was a little surprised. So Ioana has nicely delineated why patients might prefer to take 1 pill versus 3. But patients said things like, I don't feel as sick when I just take 1 pill compared to taking 3, and that surprised me. But it was a big deal to them.

The other thing that we've seen in follow-up is that adherence, not just actually taking the pills, which we know that's easier, but getting the prescriptions filled has been easier with a combination pill. Because before, it was often going to 2 different pharmacies and 1 would lapse and the other would be okay, and we're getting insurance approval and whatnot. And so it’s been nice having it just in that regard.

Dr. McLaughlin:
So for those just tuning in, you're listening to CME on ReachMD. I'm Vallerie McLaughlin, and I'm here today with Dr. Ioana Preston and Dr. Kelly Chin, and we're discussing new and emerging PAH therapies and approaches.

Dr. McLaughlin:
Yeah. I think that is fantastic. It's great to have those patient-level insights. The shared decision-making is really such an important part of our practice right now. I remember that the World Symposium, the first task force to go was the patient perspective, and really, some remarkable perspectives from them. The whole nothing about me, without me, and really engaging them is important.

So, Ioana, tell me a little bit about how that's impacted your practice with the prescription of some of these medications and, in

particular, the combination pill. And we'll talk about it with other treatments today I'm sure as well.

Dr. Preston:
Yeah, Val, it's so important to engage the patient in deciding what type of treatment, how aggressive we should be. What's their concern? What are their goals? What are they worried about, what type of side effects? I think with regards to combination pill, we finally, in PAH, have joined other larger communities such as the HIV treating community where we incorporate 2 different medications in 1 pill. And what Kelly said is amazing. The psychological aspect of lessening the pill burden is very important. It's also very helpful for our clinics and our nurses and pharmacists who apply to the insurances to get these drugs approved, doing 2 versus 1 application. It lessens the burden of the PAH clinic.

Dr. McLaughlin:
Yeah. I think both of your insights for that have been just really, really impactful. And we're all experiencing this in clinic, and I think our patients have benefited from that option.

There was also another exciting therapy that was approved in 2024, so that is sotatercept. So let's talk a little about that. Maybe we'll start with Dr. Preston reviewing the mechanism of action and a little bit about the clinical trials with sotatercept, and then Dr. Chin can talk about the placement in the algorithm.

So, Ioana, you want to give us an overview?

Dr. Preston:
Yes, absolutely. So sotatercept is the first biologic in the treatment of pulmonary hypertension. It is what we call an activin-signaling inhibitor. We've known for over 20 years that the bone morphogenetic protein receptor 2 pathway, which is an antiproliferative pathway, is diminished in patients with pulmonary arterial hypertension. Whether it's a genetic mutation that's identifiable or in the absence of any genetic mutations, we know that patients with PAH have a decreased activity of the BMPR2 pathway. Now, opposing the BMPR2-GDF pathway is the activin pathway, which is pro-proliferative and profibrotic and is increased in patients with pulmonary arterial hypertension.

So in order to balance these 2 sides of anti-proliferative and pro-proliferative processes that are abnormally PAH, sotatercept binds to the activin and blocks it from attaching it to its receptor, therefore decreasing the pro-proliferative effects on the activin pathway. Now, sotatercept has been studied in a development program starting with a phase 2 clinical trial called PULSAR and followed by the STELLAR phase 3 clinical trial. And both clinical trials showed improvement in hemodynamics as well as in 6-minute walk distance, which was the primary outcome in the phase 3 trial. And in addition, several clinically significant secondary endpoints were achieved, such as the multicomponent improvement, NT-proBNP, the risk of worsening which was decreased by 84%, very significantly for a clinician, and several other secondary endpoints, including a couple of quality of life endpoints.

Dr. McLaughlin:
Yeah. Really a remarkable study, not just the primary endpoint but 8 of 9 secondaries and real consistent effect across the subgroup. So it was very, very impressive data and everyone's excited about a new mechanism of action.

But, Dr. Chin, tell us a little bit about how the task force decided to place this in the treatment algorithm.

Dr. Chin:
At the time of the World Symposium, as Ioana was mentioning, we had the trial results for the 2 main sotatercept studies, the PULSAR study, which was their phase 2, and then the n = 323 patients STELLAR study. And STELLAR had been quite overwhelmingly positive as far as hitting the endpoints, as mentioned, but what it didn't include was treatment-naïve patients at all. And only 4% of the patients in the study were on monotherapy. So that left about a third on 2-drug background therapy and around 60% on 3-drug background therapy, which it makes it all the more remarkable that it was as positive as it was. But it also meant that as initial therapy, sotatercept would not be recommended. This is where we have such solid data for the ERA/PDE5i combination, that this, as the initial up-front therapy for the majority of patients, the not high-risk patients, would continue to be recommended. And then triple therapy, including a parenteral prostanoid, recommended for high-risk patients at diagnosis.

So then for follow-up, this was clearly where sotatercept was going to be recommended, but exactly in whom and how to position it was the real challenge. Ideally, there would be head-to-head studies, because that's the best way to compare which medication is best, and also, ideally, long-term studies. But lacking that, as we often do in pulmonary hypertension, we went through as many studies as we could identify that included patients on background therapy, because we're not looking at the initial treatment but follow-up treatment, needed to be randomized and then, also, ideally, blinded. But that comes up with one study that was only partially blinded. And in this category, there are studies for oral and inhaled treprostinil, oral selexipag, and then the switch study of riociguat, which was randomized

but unblinded.

So going through these studies and putting sotatercept into context with these other medications, I think, is the challenge that we're going to have moving forward. From the World Symposium standpoint, we discussed the positives from the studies, the negatives, including adverse events or limitations in the endpoints that were looked at, and in the end, came up with relatively stronger recommendations for patients who were already on triple therapy, because this is the next available therapy, and this also matched most accurately the patients who were actually in the studies and STELLAR with 60% on triple therapy.

For patients who are on 2 medications and looking to add on third therapy, we have different recommendations for the intermediate-low versus intermediate-high and high risk.

The best treatment options for patients at high or intermediate-high risk at this time appear to be sotatercept or parenteral therapy with a prostanoid. And in particular, for the highest risk patients, if they are not already on a parenteral prostanoid, that was recommended.

For the intermediate-low-risk patients, that's where there's a lot of balancing between the drug delivery, the side effects, the patient characteristics, and their goals, and I think is a great place for shared decision-making to make the ultimate decision for the patient.

Dr. McLaughlin:
Yeah, Kelly, that was a wonderful summary of what the algorithm looks like, and of course, in these meetings, we look at papers and we have inclusion/exclusion criteria in papers, but of course once it's out into the real world, we think about how we apply it in our practice. And let's all face it: Not every single patient in our practice meets all the inclusion and exclusion criteria of a clinical trial. So we then have to translate that into clinical practice.

So, Dr. Preston, maybe you could tell me a little bit about how you're using sotatercept in your clinical practice currently.

Dr. Preston:
So, Val, so to remind our viewers, sotatercept is given as a subcutaneous injection every 3 weeks. The patients need to learn how to prepare the medication, so there's a mixing protocol that patients are being taught by the specialty pharmacy, and the most of them deliver the injection at home every 3 weeks. Now, the practitioners should know that the recommendations are to check complete blood count, especially hemoglobin and platelets at baseline as well as before each dose. So every 3 weeks for the first 5 doses, and then thereafter periodically to check with blood counts. Because the possible side effect profile of sotatercept includes an increase in hemoglobin, a decrease in platelets. And also, a couple of other side effects that we've learned during the clinical trials are the occurrence of telangiectasias that usually occur later on in the treatment, so not immediately after the start of therapy. But also, there is an increased risk of bleeding that the practitioners should be aware of.

Dr. McLaughlin:
Yeah. And so again, the shared decision-making is important to go through all those practical points and the side effects, which are not trivial and need to be placed in context with the patient, as well as how effective the therapy is. And so there's, at least in my experience, there are many patients who come in asking for it because there's a lot of hype about it on social media and the like. And I still have a lot of patients who kind of say, I'm doing really well where I am. It's a new drug; we don't know about the long-term effects. I think I'm happy where I am. And everything in between as well. So again, it's a good place for shared decision-making and the importance of what the patient's goal is, what the rest of the patient profile is, like, are they are particular high risk for bleeding, or how far off are they from their goals? So really an important conversation to have with the patient.

Now, the STELLAR trial was Functional Class II and III patients, and we know the ZENITH study also was positive. The ZENITH study, which was looking at a much higher-risk population, patients with more advanced symptoms, and a high REVEAL risk score. And so that's great data to complement the profile that we have on sotatercept.

Do you want to give me your thoughts on that? On the ZENITH trial, Ioana?

Dr. Preston:
Yes. So ZENITH was geared at evaluating the efficacy of sotatercept in higher and more advanced PAH patients, and those are patients at high risk of side effects, of hospitalizations, and worse mortality. So patients were enrolled in the ZENITH trial if they had a REVEAL score of 9 or above, so that's high risk. So, really, we're talking about really advanced patients on background therapy. So in spite of background therapy, these patients really needed treatment.

Now, ZENITH was positive before the trial ended because there was a significant impact on the outcome in patients treated with sotatercept, so the trial ended early. And that tells us that it is a pretty potent medication, that the benefits/side effects profile is really to where it's a benefit for these patients.

Dr. McLaughlin:
Right. And very important, right? And again, you are making comments about risk and benefit. And, Dr. Preston, you alluded to some of the safety signals a little bit earlier, but let's take a moment to dig into those a little bit more. So bleeding is an important one. More than 20% of patients treated with sotatercept have some bleeding. It's mostly sort of nosebleeds, nuisance nosebleeds, but there have been some other more serious bleeding events that have occurred. There are the telangiectasias that have occurred as well, so we need to keep that in mind. Of course, the impacts on the hemoglobin, which can go up, and the platelet count, which can go down.

So now that we've had experience with this drug, I think we were all in the clinical trials and we've had commercial experience for nearly a year now, tell me a little bit about your approach, Dr. Chin, to the safety, and are there any populations that you're specifically a little more concerned with? Like, for example, those patients who are on prostacyclins who already may have a low platelet count or more of a bleeding risk.

Dr. Chin:
So when we very first started using sotatercept, the amount of safety data that we had was a bit more limited. We had what was in the STELLAR trial and then some data from the open-label extension. But the open-label extension study has continued on and then, as well as with ZENITH and HYPERION ongoing, we've been able to see over time what happens to rates of the elevated hemoglobin, the low platelets, and the bleeding risk. And it does look like these are generally reassuring, which as you said, most of the bleeding is things like nose bleeds and occasionally more serious things like GI bleeding, and, fortunately quite rarely, things that are even more serious like hemoptysis or CNS bleeding. But they're still a factor, and so I think when we first started, we went through every patient that was referred to or on the transplant list and looked at them for potential candidacy. They were my first patients to go on sotatercept. And then as time has gone on, we've moved into lower-risk patients, but at the same time continuing to assess this bleeding risk and looking for patients who may be at high risk.

I think the patient with low platelets on prostacyclins is a particular concern. That's the one that I struggle with the most. I have patients whose platelets are hovering around 50, but on a bad day when they get a line infection or just anything, they might drop from there. And yet they're not doing well from their pulmonary hypertension. And so that one's a particular challenge. I'm looking at those patients usually as transplant candidates as well, but I think it will be nice over time to gather more data in the people who did choose to go ahead with sotatercept. And right now, I'm a bit hesitant, but what happened to those folks and continue to watch the safety really closely there.

Dr. McLaughlin:
Yeah, what wonderful insights. And the whole concept of shared decision-making, all the things we need to consider, there's a lot of topics to cover. There's the patients who are at intermediate-high risk, who, before sotatercept, we would have pretty clearly set a parenteral prostacyclin. Many of them would rather try sotatercept as opposed to a parenteral prostacyclin. How do we feel about that? Are there any factors, not only in terms of safety, but in efficacy that come to mind? The patients with a really low cardiac output, for example. I'm still wanting to see a parenteral prostacyclin in those patients who we think about the more long-term events versus just how you feel in the next 6 months. Again, we're still collecting data. The bleeding risk, the interactions with some of these other drugs, there's just so much to consider. And I think probably we're all going to say every patient is individualized.

But maybe, Dr. Preston, Dr. Chin, you can just give us a couple pearls as you approach these patients in clinical practice.

Ioana, you want to start?

Dr. Preston:
Yes. As you said, I think we're getting closer to practicing more of an individualized medicine now that we have that many options, and we're lucky to have options for our patients. But their phenotypic profile, their wishes, and their comorbidities, they all have to play a role. And also, it sometimes is difficult to recommend or to strongly recommend one treatment versus the other and shared decision with other specialty healthcare providers and their input, and doing a roundtable in your clinic with other specialists, I think, has a lot of value. From the GI specialist, who has done an endoscopy on a patient and has seen the stomach and what was maybe a remote bleeding that we should take into account, to why are the platelets on the low side? Not too low, but slightly low. Do we put them at risk for even lowering platelets with sotatercept and so on. So I think we have developed our clinical practice to be nuanced, but we also need help from our colleagues and definitely input from our patients.

Dr. McLaughlin:
Kelly?

Dr. Chin:
Yeah. I would echo many of the things that Ioana said and add to that that I'm really trying to use shared decision-making, not just in the

treatment algorithm specifically, but more globally as well. So stepping back sometimes and asking patients what their goals out of this visit are today and what are their goals for their health in the coming year, and so on. And I'm sometimes very surprised at the answers that I get there. Things that I might not have thought of. Even a patient who was given an exercise restriction at diagnosis, who now we're months later. They were passing out; they're not anymore. And they hadn't realized that, oh, hey, it would be okay to expand on what we're doing now.

Dr. McLaughlin:
Yeah. That's a great point.

Now, we've talked a lot about new medicines. There's a tremendous amount of excitement about it. We've come so far in the medical therapy for pulmonary arterial hypertension, but we would be remiss if we didn't talk a little bit about lung transplantation and where it falls and how we prepare patients for that. Sometimes we need to bring up topics that need to be addressed well before the patients become transplant candidates, things like weight or smoking or what have you.

And so maybe, Kelly, again, where that fell in the treatment algorithm, tell us a little bit about how we should approach lung transplant and if you think some of these newer agents are going to delay transplantation further in some of our patients.

Dr. Chin:
Yeah. What an exciting time with these agents that may do just that. The timing of transplant referral turned out to be one of the surprisingly contentious topics at the World Symposium. The transplant clinicians there are concerned that many patients are referred at a time point when it may be too late for transplant. And this turned out to be not just because they were too sick, which is what I think we usually think about, but also for things like establishing who their caregiver was going to be and what city are they going to live in and whether they needed to lose weight before transplant and these types of things.

So we had a lot of conversations about this that I think were really helpful. They felt that all patients at high risk should be referred for transplant at diagnosis and that there was little harm to that. I personally feel that it can be harmful, though, because it's not only expensive but frightening and more tests, and even just having – if our patients are coming from far away, it's not a small ask. So in the end, what the algorithm says is consider transplant referral at diagnosis, taking into account patient factors, center factors, and how long the transplant referral process is likely to take. And then, in addition, I think we put into the paper a really important table, which is some of the things that one needs to be thinking about at diagnosis that may be barriers to transplant that you really should be getting on from the beginning. Is your patient smoking or using drugs? Are they overweight? All of these things may take time to address, and they would be good for their health anyway, so we should all be addressing them and thinking about it.

Dr. McLaughlin:
Yeah, I think that was a great summary, Kelly. It was a bit contentious, and I do think that a patient with a new diagnosis of IPAH or PAH is really overwhelmed, especially if they're that sick, so you make really good points. But we also know that a lot of them are going to get a ton better with IV therapy, and so I think the happy medium you so elegantly struck with both of those task forces was very, very on point.

So we are running towards the end of our time, and I think it's important to highlight a few overarching principles. I think the one that I would want to highlight the most is really being methodical about the diagnosis, make the right diagnosis, understand what may and may not be attributed to comorbidities, and then, also be willing to reevaluate that as you go down the treatment pathway with our patients.

Maybe I'll ask Dr. Preston and then Dr. Chin to give one takeaway pearl in addition.

Dr. Preston:
I would say, Val, in the journey of treating pulmonary hypertension, I think we need to be proactive, and we need to be on the ball. We need to follow the patients on a regular basis, even when they're doing well, and ensure we're achieving both patient's goals, but our goals, clinical goals, and match them together.

Dr. Chin:
My take-home point is similar and it's be vigilant with the timing of risk reassessment and, when needed, therapy escalation. We know from observational studies, from large cohort studies, that there's often really big delays from the time a patient is not doing well and the addition of even oral therapies, let alone parenteral therapies. And yet, we know how effective these treatments can be. So timely follow up and, when needed, therapy escalation.

Dr. McLaughlin:
Well, I thought this was a wonderful discussion. As always, I learned something from both of you, Dr. Preston, Dr. Chin. It was

wonderful to speak with you.

I'd like to thank the audience for joining in today. And again, thank you, Ioana and Kelly, for sharing all of your valuable insights and expertise. It was just such a wonderful conversation today.

Dr. Preston:
Pleasure to be here.

Dr. Chin:
Pleasure as well. Thank you.

Announcer:
You've been listening to a replay of a live broadcast discussing new and emerging therapies for PAH and why making the right diagnosis is key when determining your treatment approach. This activity was provided by Total CME, LLC and is supported by Actelion Pharmaceuticals US, Inc., a Janssen Pharmaceutical Company of Johnson & Johnson.

To receive your free CE credit or to download this activity, go to ReachMD.com/CME. This is CME on ReachMD. Be Part of the Knowledge.