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Pulmonary Hypertension Management: Practice Trends and Updates

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Chapter 1: Update in Pulmonary Arterial Hypertension Therapies

Dr. Moles:
So the first message that I want to transmit to everybody is that nowadays we have several treatment options that are available for the management of pulmonary arterial hypertension.

In this simplified graph, where you can see on the left side is the landmark trial led by Robyn Barst that led to the approval of IV epoprostenol, or Flolan at that time, in 1995. And all the different clinical trials that led to the approval of medications in the United States, and more recently in 2023, STELLAR and A DUE, which led to the approval of sotatercept and the combination pill of tadalafil and macitentan by the FDA in 2024. In this year, we have 16 FDA-approved medical therapies available to manage patients with pulmonary arterial hypertension.

So this is a great graph that I think updates what we know in terms of the pathways of therapy for PAH. On the right side of the screen, you will see the traditional pathways that predominantly affect the vascular tone. Those are pathways like the prostacyclin pathways, the nitric oxide pathway, and the endothelium pathway. And on the left side of that graph, what you're going to see is the more novel pathway, which affects predominantly vascular proliferation, which is the activin signaling pathway, where sotatercept is predominantly acting.

So noted for and to understand how the activin signaling pathway acts, I need to get a little bit more molecular for a few seconds here. So on the left side of your screen, what you're going to be seeing is this pathway has 2 main receptors. One is called the ACTR2 receptor. This receptor is activated by activins, and when it is activated, it leads to a pro-proliferative state in the pulmonary vasculature. On the other hand, we have the BMPR2 receptors. When activated, they lead to an antiproliferative state. And in patients who have PAH, this BMPR2 receptor is not working properly, leading to an imbalance towards the pro-proliferative state.

Now, sotatercept, the way it works, it binds to activin, and by doing so, it leads to a lesser activation of the ACTR2 receptor, and in that way, leading to a rebalance of that proliferative and anti-proliferative status of the pulmonary vasculature.

So sotatercept was studied in a phase 3 clinical trial called, STELLAR. STELLAR was presented in 2023. The patients in STELLAR were, in their majority, prevalent patients with an average time to diagnosis of about 8 years, and they were very well treated. 60% of them were on triple combination therapy, and about 40% of them were receiving parenteral prostacyclin. And what STELLAR showed was that the 6-minute walk distance, which was the primary endpoint, was significantly different in those patients who were assigned to sotatercept compared to those patients who were assigned to receive placebo. And as you can see, that benefit in the 6-minute walk

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distance was seen very early on, even at the third week after receiving the first dose of the medication.

Now STELLAR had 9 prespecified secondary endpoints and 8 of them were positive. They included NT-proBNP changes, pulmonary vascular resistant changes, composite endpoints. And what I think is really important is that the time to death or clinical worsening events was delayed in the patients who received sotatercept. And I think this is important because this is a small clinical trial, that even though it was small, we could see that significant difference in morbidity/mortality outcomes that so much matter to patients.

In March of this year, the FDA approved sotatercept for the management of PAH.

Now, I mentioned to you that the mechanism of action is quite different in sotatercept because it predominantly affects vascular remodeling rather than vascular tone, and traditional medications that we used to use for pulmonary arterial hypertension tend to reduce pulmonary vascular resistance by decreasing a little bit the pulmonary artery pressure, but predominantly increasing the cardiac output.

And what we have learned about sotatercept so far is the hemodynamic profile is quite different. The decreasing PVR is predominantly led by a decreasing mean PA pressure, but the cardiac output remains quite the same. Now, despite the cardiac output staying the same, there's not only an improvement in mean PA pressure but the pulmonary artery compliance, the biventricular work, and even the right atrial pressure are positively affected by this medical therapy.

In terms of imaging and RV function, what we have seen is that by echocardiography the right side of the heart, the right ventricle, decreases in size quite dramatically. Now, the function is also affected in a positive way by an increase in right ventricular fractional area change, but not so much on TAPSE changes. Despite the TAPSE not being significantly affected, the pulmonary right ventricular to pulmonary artery coupling is significantly improved by the improvement in pulmonary artery pressures.

Now, another study that I think is significant for patients with PAH is A DUE. This is a study that looked at the safety and efficacy of a combination pill of macitentan and tadalafil in patients who are both treatment naïve or who were previously treated with an ERA or PDE5 inhibitors. And they were randomized to receive this combination pill of tadalafil and macitentan, or macitentan monotherapy, or tadalafil monotherapy. The primary endpoint was a change in PVR at 16 weeks, and that was significantly improved by the combination of macitentan and tadalafil in one pill rather than each monotherapy alone. The medication was well treated, and this also led to the FDA approving this medication in March of 2024. Now I think that less pills can potentially improve medical adherence in patients who are receiving multiple medical therapies. So I'm excited about this possibility.

I want to focus a little bit on up-front triple combination therapy, and this is something that we consider when we are faced with the patients who are at the highest risk for cardiovascular events. And the message that I want to transmit to use is that not all up-front triple combination therapy is equal.

So what you're seeing here is data from the TRITON trial. The TRITON trial was presented in 2021. It randomized patients who were treatment naïve who were recently diagnosed with PAH, and they were randomized to receiving an initial up-front triple combination therapy with tadalafil, macitentan, and selexipag, which is an oral prostacyclin receptor agonist, versus an initial double combination therapy with tadalafil, macitentan, and placebo. And the primary endpoint at 26 weeks was a change in pulmonary vascular resistance. As you can see on your right, there was no difference in either group. Now what's important in what we learn about this trial is that the combination of tadalafil and macitentan, when given up front in the treatment, leads to a quite significant reduction in pulmonary vascular resistance of about 50%. So in general, if you're thinking about an up-front triple combination therapy, using selexipag may not be the right choice.

On the other hand, I want to talk about triple up-front combination therapy with a parenteral prostacyclin, and what I'm showing you here is data from the French Pulmonary Hypertension Network and Registry. As you know, France has a very well-kept registry of all their pulmonary hypertension patients and the treatment they receive. And this is a retrospective analysis of the patients who had idiopathic, heritable, or anorexigen-induced PAH that enrolled between 2006 and 2018. And they looked at 3 different groups. One was the patients who were started on a triple combination therapy with a parenteral prostacyclin, patients who are started on a dual combination therapy, or those who were started on monotherapy. And what you can see on the right and upper portion of the screen is that those patients in red had a very good long-term survival. Those were the patients who were starting on triple up-front combination therapy with a parenteral prostacyclin.

Now, when you look at the risk profile at baseline, this group was the groups that was predicted to have the worst prognosis. And what you can see is that that group that was started on a triple combination therapy with the parenteral prostacyclin at the first follow-up was a patient that was able to achieve a lower risk right away. So in general, if you're thinking about patients who have a high risk for cardiovascular events, considering triple up-front combination therapy with a parenteral prostacyclin may be the right strategy.

Now, I want to conclude, saying that many therapies are available for the management of PAH in 2024. The activin signaling pathway is

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a novel therapeutic target for the management of this condition. Sotatercept is FDA-approved in PAH and has a distinct hemodynamic effect that we're going to keep on learning and know how to apply this knowledge to our clinical practice. The combination pill of tadalafil and macitentan is now FDA-approved, and I think there is a space here to improve adherence with our patients. And not all triple up-front combination therapy is equal, and if you have a high-risk patient at the time of diagnosis, considering a combination including a parenteral prostacyclin is probably the right thing to do.

Chapter 2: Updated PAH Treatment Algorithm

Dr. McLaughlin:
I would like to take you through the updated recommendations for the management of patients with PAH based on the 7th World Symposium.

As you may know, we have World Symposium approximately every 5 years, and the most recent one was held in late June, early July in Barcelona, Spain, and there was a task force dedicated to an updated treatment algorithm. This is a consensus-based recommendation. It's not a full evidence-based recommendation, but it's a pleasure to share this with you. And I wanted to start out by some of the supportive measures because sometimes we get so deep into medications that we forget about some of the basics.

So supervised exercise training is very important, and in fact, there are some studies that show that pulmonary rehab helps the patient as much in terms of improvements in hall walk as some of our medications. So it's important to make sure that we offer this to our patients once they are on PAH-specific medication. So that's very important, supervised exercise training.

As you know, this is a devastating diagnosis and many of our patients need psychological support, so it's important to remember that. It's important to keep up to date on immunizations. These are all important infections that can occur and it can knock any of us down, but certainly these patients have less reserve and are impacted oftentimes by infections such as COVID, influenza, strep, and even RSV, and we now have a vaccination available for that.

Volume management is something that is very important to do. It's obviously a challenge. The patients don't like to take diuretics and go to the bathroom all the time or watch their sodium, and it can be very labor intensive for sites, but it's very important to keep track of their volume status and adjust diuretics when appropriate.

Hypoxemia further causes pulmonary arterial vasoconstriction, so it is important to manage their oxygen. Consider oxygen supplementation for those who are hypoxemic. And it's important to remember not just at rest, but also exercise, sleep, and altitude as well. There's not great data for iron deficiency. We certainly think it applies just like we see it apply in heart failure, but it is certainly something that we check and we offer iron repletion to patients who have iron-deficiency anemia.

There's a lot that goes into counseling women of childbearing potential. We recommend against pregnancy, and we recommend clear contraception because the hemodynamic stresses of pregnancy in patients with pulmonary arterial hypertension can be life-threatening. And this is a challenging topic, and in fact, Dr. Preston led one of the task forces that dealt with some of these special issues such as pregnancy.

And then it's important to consider pretransplant counseling. We certainly have wonderful medications these days, and a smaller proportion of our patients get to transplant than they did perhaps 10, 20, 30 years ago. But some of our patients still need transplant and it's important that they know that this is an option. And even to introduce some concepts so that they can prepare for transplant in the event that they need it. Things such as trying to obtain ideal body weight. If someone needs a transplant and they're 50 pounds overweight, it's going to take a while for them to get to the weight they need to be. Or smoking cessation. Most programs won't transplant someone unless they have been off of tobacco for 6 months or so. So it's important to address those issues so that patients can prepare for that.

This is an overview of the treatment algorithm that was proposed at the time of the 7th World Symposium. There are a number of key concepts here. One is that the evidence really applies to patients with idiopathic, heritable, drug- and toxin-induced, and CTD-related PAH. So it's really what the treatment algorithm applies to. Even though Dr. Moles, Dr. Preston, and I can talk about how we often use something very similar to this in patients with HIV or congenital heart disease, and the reality is we tend to apply this to those patients. And I think the key is, you do the initial risk assessment and make that initial treatment decision, and we have lots of evidence behind that, but really, what leads to success is that frequent follow-up, that reassessment within 3 to 4 months and trying to get the patient to a low-risk status. And we certainly have wonderful risk assessment tools here.

So I think the other thing to highlight, in addition to the subtypes that this applies to, is that we also need to remember that most of the trials that led to the therapies that we currently have available used the old hemodynamic definition of a mean PA greater than or equal to 25 with a PVR greater than 3 as entry criteria. So that's really who this treatment algorithm applies to.

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I think we also have to highlight the importance of risk assessment, and we've learned so much about risk assessment over the years and we can do a more detailed risk assessment at the time of the initial evaluation because oftentimes we have more data, including a right for catheterization at that time.

But we also have lots of risk assessment tools that rely on noninvasive data, including functional class, hall walk, and natriuretic peptides to do objective risk scores. But even as we go on and we follow a patient longitudinally, it's very useful to use imaging, including echo or CMR and hemodynamics to complement that risk assessment.

So let's talk about that very first risk assessment, that time of diagnosis. And what this algorithm does is divide patients into high risk or not high risk, and the not high-risk group on the left, there is an abundance of data to suggest that combination therapy with an ERA and PDE5 are useful for optimizing outcomes in patients with lower-intermediate or, basically, not high-risk findings. The high-risk group, these are patients who calculate to high risk, but I think it's also important to remember that some patients who might calculate to intermediate risk using 3-strata but have a very low cardiac index or florid right heart failure, those are patients that could be considered for initial combination therapy that includes a parenteral prostacyclin as well. And Dr. Moles went through some very important data regarding that.

Here's a list of the therapies that we currently have FDA-approved, and he went through this in some detail, so I will not belabor it.

But I do want to highlight this paper which Dr. Moles also highlighted in that the risk assessment is critical in making treatment decisions, and initial triple combination therapy is superior to other strategies in patients at high risk, which we have some different observations for, but in this paper, also patients at intermediate risk. So I want to remind everyone that there's a lot to risk assessment, and some patients at intermediate risk still might benefit from more aggressive therapy at the onset.

The algorithm then goes on to say the important next step is a reassessment at 3 to 4 months and that should be repeated frequently. And again, we have noninvasive tools that will get functional class, hall walk, and natriuretic peptides, but oftentimes we gather other information, including hemodynamics at RV imaging. So let's say we now do that first risk assessment. What category does the patient fall into?

And we've learned a lot about risk assessment and how big that intermediate-risk group is, and there are now tools to divide that intermediate-risk group into intermediate-low and intermediate-high. So we now have 4 different categories at that first reevaluation timepoint.

So patients who meet low-risk criteria on the initial therapy choice tend to do very well. Their prognosis is very good, and in most cases, we really don't need to add anything else. We just continue their therapy as it is. The patients who are at intermediate-low risk, they're still not where we want them to be, but they are not at particularly high risk. Their prognosis is better than intermediate-high or high, and we have a number of choices for these patients.

I think the key thing here is that patients who are intermediate-low risk, we're not so worried that we need to go straight to a pump, to a parenteral prostacyclin, and so we have other options, including an activin signaling inhibitor, and Dr. Moles reviewed the data on this new agent very nicely. And then, there are other options of less aggressive prostacyclin, so oral and inhaled prostacyclin pathway agents, and we can also consider switching from a PDE5 to an SGC.

Patients at intermediate-high risk, their prognosis is poor. They're actually much closer to high risk than they are to low risk, and so we do recommend additional therapy in those patients, which might be with a parenteral prostacyclin if they were not placed on one at the onset, or an activin signaling inhibitor. And those who are at high risk, the parenteral prostacyclin is a first choice if they're not already on it. One can consider an activin signaling inhibitor as well.

But the other thing that's very important to remember is that patients who remain at intermediate-high or high risk despite combination therapy really should be evaluated for lung transplantation.

Now, I would like to share another treatment algorithm. This was really another consensus-type document that was published by a number of US investigators and experts that look at it a little bit differently. And so again, diagnosis and high risk needs parenteral prostacyclin therapy, and either low or intermediate risk gets combination oral therapy with ERA/PDE5. Again, noting that there might be intermediate-risk patients with high-risk hemodynamics for whom we might consider a parenteral prostanoid.

And then it divides the follow-up quite similarly to low risk on the far left, with the caveat that someone may be low risk but have high-risk imaging or high-risk hemodynamics. These tend to be the younger patients, and we're worried about their longer-term prognosis, and so even though they meet low-risk criteria, we might get a little more aggressive with them and treat them as we do the intermediate-low-risk patients for whom we have similar options, including an activin signaling inhibitor, a non-parenteral prostacyclin pathway agent, or

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replacing a PDE5 with an SGC. And then, of course, the intermediate-high-risk patients, we have activin signaling inhibitor or parenteral prostacyclin. And really highlight the importance of shared decision-making with patient input.

And then, on the other side we have similar recommendations at follow-up for patients who are already on parenteral prostacyclins, including continuing as they are if they're meeting low-risk status and potentially adding an activin signaling inhibitor if they remain at intermediate-low or intermediate-high or high risk despite the parenteral prostanoid and the dual therapy that they're on. And then, again, acknowledging the importance of lung transplantation evaluation in this population.

So as I mentioned, that algorithm that I covered is really specific to patients who have been included in clinical trials but there are many patients that we see that don't entirely fall into that range.

Chapter 3: PAH Special Circumstances: Mean PA 21-24 mmHg

Dr. Preston:
So let's look at the hemodynamic criteria for the definition of pulmonary hypertension, which has changed.

If we look at all the clinical trials that both Victor and Val alluded to, they included patients in the older hemodynamic definition, which had a mean PA pressure of 25 or above and a pulmonary vascular resistance, or PVR, over 3 Woods units. However, recently, the data from several researchers and papers recommended that the hemodynamic criteria for pulmonary hypertension are changed.

So let's look at this table. Pulmonary hypertension is defined by a mean PA pressure of over 20, instead of 25, mmHG, as well as a pulmonary artery wedge pressure of 15 or less, which has been the same as before, but also with a pulmonary vascular resistance, or PVR, over 2 Woods units. So this precapillary pulmonary hypertension hemodynamic definition applies to pulmonary hypertension of Groups 1, 3, 4 and 5. And we have to understand the new hemodynamic definition.

The pulmonary hypertension in Group 2 secondary to or associated to left heart disease is broken down into isolated postcapillary PH, or IpcPH, and combined post- and precapillary PH, or CpcPH. And you can see the hemodynamic criteria. The mean PA pressure over 20 and the pulmonary artery wedge pressure over 15, which characterizes increased filling pressures on the left side. And on the postcapillary, the PVR is 2 Wood units or less, and the combined PVR is over 2 units. Also interestingly, what the World Symposium for pulmonary hypertension recommended was to reintroduce the definition of exercise pulmonary hypertension, which is a mean pulmonary artery pressure by cardiac output slope of over 3 between rest and exercise. And this is a new addition to our previous definitions of resting pulmonary hypertension.

What I wanted to point out is that noninvasive methods such as echocardiography or cardiac MRI lack precision or are not sufficiently validated to accurately assess pulmonary hemodynamics. So in order to really diagnose pulmonary hypertension of different groups and different etiologies, you really need a right heart catheterization.

So moving on. The World Symposium for pulmonary hypertension that Dr. McLaughlin just recently mentioned introduced early pulmonary hypertension definition, which means a pulmonary artery pressure of 21 to 24 and/or a pulmonary vascular resistance of 2 to 3 Wood units. And this is the group of patients that have not been studied in the era where the previous definition for pulmonary hypertension was included and were readily included in the new definition.

So let's look, what does early pulmonary hypertension mean? In the era before the hemodynamic definition had changed, we used to call it borderline pulmonary arterial hypertension, so anywhere between 19 to 24 or 25. So if you look at this particular study and cohort of large patients, patients who had a higher mean pulmonary arterial pressure had an overall survival. And this cohort includes patients with different etiologies of pulmonary hypertension. And regardless of the etiology, the higher the pulmonary hypertension, the worse the outcome.

And then, on the left-hand side, you see the cutoffs of the mean PA pressures, and on the right-hand side, you see the definition at the time of the study, which showed lower normal mean PA pressure, upper normal borderline PA pressure, or resting pulmonary hypertension which was the older definition. So if you look at those 2 graphs, it seems to be a continuum of worsening PA pressures worsening survival.

And a second study looked at a large cohort that qualified patients in mean PA pressures over 25, so the old definition of pulmonary hypertension, versus borderline PA pressures between 19 to 24, versus the black line which showed patients with normal mean PA pressure. And over time, from the time of the right heart catheterization assessment, the outcome was worse as the PA pressures were worse. And if you look on the right-hand side, the adjusted mortality was the same, the higher the pressures, the worst the survival. And the difference between sexes suggested that men had a little bit of a lower mortality compared to women.

However, the consequence of higher PA pressures were clear, that they were associated with worse survival. But does that matter if a

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patient of yours has a borderline mean PA pressure elevation? Meaning, between 19 to 24, or 20 to 24.

It seems that it does because if you look at this cohort that had an initial right heart catheterization that had mean PA pressures between 20 and 24, the majority of these patients progressed to resting pulmonary hypertension. And you can see that in the blue lines where patients develop overt pulmonary hypertension at the follow-up. So the presence of borderline or early pulmonary hypertension should raise a red flag that this condition, and this is hemodynamic, that abnormality, may be associated with worse prognosis and resting pulmonary hypertension in the future.

And if we look differently, if we look at the survival of pulmonary hypertension by the pulmonary vascular resistance – this is a very large VA cohort; the majority of these patients were males. But if you look on the left-hand side, they're all patients with mean PA pressures of at least 19. And as the pulmonary vascular resistance increased, mortality increased.

In the middle graph, it shows a vastly increased mortality in patients with precapillary pulmonary hypertension, with a wedge pressure of 15 or less, where this tip of the mortality is much higher as the pulmonary vascular resistance increases, and this is not as significant, not as dramatic, as patients who probably have left heart disease and pulmonary hypertension in the left graph.

So let's move on to other cohorts that can give us a glimpse on the survival of patients with what we call early pulmonary hypertension. This is a UK-based national database that surveyed patients who underwent the right heart catheterization for different reasons. And you can see the breakdown of a mean PA pressure of less than 21, mean PA pressure of 21 to 24 in the blue, and mean PA pressure of over 24, which is the old definition of resting pulmonary hypertension. So over almost 3,000 patients, if you look on the left-hand side, depending on the pulmonary vascular resistance, the higher the pulmonary vascular resistance, the higher of mortality. The PVR between 2 and 3 is right in the middle, but it's worse than a normal pulmonary vascular resistance. And on the right-hand side, you can see the effect of the mean PA pressure in patients who had a pulmonary vascular resistance between 2 and 3, and the higher mean PA pressure, the worse the survival. These data and results were independent of age, sex, and the presence of lung or heart disease.

So it’s not only in the large cohorts that include patients with Group 1 or 2 or 3 disease, but also if we look within the Group 1 PAH patients. And we know that scleroderma PAH is a very important entity and subgroup within the PAH category. So if we look at the mild pulmonary hemodynamic alterations in patients with systemic sclerosis, depending on the pulmonary vascular resistance, their outcomes is very affected by their hemodynamics. So if their PVR is 3.6 or above in the orange or red lines, their 3-year survival is 50%. But also, if you look at the PVR around 2.3 in the green lines, that survival is worse than the survival of patients who have normal pulmonary vascular resistances. So mild pulmonary hypertension and systemic sclerosis seems to have a significant impact in survival of these patients.

And it's not only in systemic sclerosis, but in cirrhotic patients in whom we know they develop portal pulmonary hypertension. So if you look on the right-hand side, this is a group of patients who have been evaluated for portal hypertension and they underwent a right heart catheterization. And among the patients on the right-hand side of the flow chart who were diagnosed with pulmonary hypertension but they were untreated, if you look on the right-hand side, for out of 16 patients, 9 patients developed overt pulmonary hypertension. They started off with a pulmonary vascular resistance between 2 and 3, but more than half developed overt pulmonary hypertension. And if you look at the right-hand side graph that shows baseline versus follow-up pulmonary vascular resistance, the untreated patients in this category tended to increase their pulmonary vascular resistance, suggesting that once established, pulmonary hypertension in different subgroups, such as portal pulmonary hypertension, evolves and increases.

And then, lastly, we talked about early pulmonary hypertension. However, I wanted to allude it to exercise PH. And why was exercise PH included in the definition of pulmonary hypertension at our last pulmonary hypertension symposium? Because exercise PH is associated with increased cardiovascular event-free survival. And if you just look at the graph which shows patients with no pulmonary hypertension in blue versus patients with exercise-induced pulmonary hypertension and rest pulmonary hypertension, the presence of exercise-induced PH is associated with worse cardiovascular event-free survival. I would like to remind you, the definition of exercise-induced pulmonary hypertension is an abnormal PA pressure cardiac output slope over 3 that has been included in the World Symposium definition. So this is something that needs to be evaluated and kept an eye on.

So what don't we know about early and about exercise pulmonary hypertension? We really need further refinement and study in the future. However, if we look at all currently available drugs for the treatment of PAH that both Victor and Val very eloquently presented to you, and also chronic thromboembolic PH or PH associated with lung diseases, all these drugs were approved based on clinical trials using previous hemodynamic definitions of pulmonary arterial hypertension that were characterized by a mean PA pressure of 25 or above, a normal wedge, and a pulmonary vascular resistance of over 3 Wood units.

So where are we at? We know that early PH as well as exercise PH are entities associated with worse outcomes compared with normal population. We know that in many subpopulations, early pulmonary hypertension progresses, so we need to be aware of this entity. And

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presently, the treatment of patients with early pulmonary hypertension with specific therapies is not currently recommended due to the absence of sufficient data from clinical trials. But I have to say, I'm very hopeful and optimistic that further and future research will give clues on this topic.

Chapter 4: Q and A Session

Dr. McLaughlin:
Well, Ioana, that was really fantastic. Thank you very much. And, Victor and Ioana, we have a number of questions that have come in and we have plenty of time to address some of these questions.

Ioana, I'm going to throw this first one to you because you've been in PH a long time, you've been educating people a long time, and this one really has to do with how entry-level clinicians can keep up with the current guidelines for the management of patients with pulmonary hypertension. Obviously, the ERS/ESC guidelines came out a couple years ago, 200-and-some pages long. The World Symposium is a whole issue of the ERJ with 15 chapters. Tell me how you recommend clinicians who may be more junior, or may be not focused their entire life on pulmonary hypertension, keep up with the important concepts.

Dr. Preston:
Yes, and, Val, this is an excellent question because both as pulmonologists and cardiologists, we encounter pulmonary hypertension very often in our clinics. And it's not only Group 1, but if we think about Group 2 and Group 3 and Group 4 and so on, we have a lot of patients with different forms of pulmonary hypertension. My recommendation is to keep up with the latest guidelines. And I think the 7th World Symposium pulmonary hypertension recommendations are very pragmatic and very hands-on that a clinician can use in their clinical practice. The other aspect is to connect with your specialists. If you are a pulmonologist, talk to your cardiologist to look for signs and severities of pulmonary hypertension when he or she reads the echocardiography that you order. Connect with the rheumatologist to make sure that they screen patients, just one or two a year, patients with scleroderma. But I think they're so important to pick up so we can offer early treatment because you could see that mild elevations of pulmonary hypertension, of pulmonary pressures, are associated with worse outcome.

So develop a multidisciplinary team with interest in pulmonary hypertension that can help the young clinician to build a consistent algorithm to screen and treat these patients.

Dr. McLaughlin:
Yeah, I think that's all great advice. Obviously, there are a lot of educational programs such as this that try to summarize things in a reasonable period of time, and there are many PH centers that are happy to form relationships with more community-based centers or other practices that might be on more of an entry-level in terms of pulmonary hypertension. So that's all great.

Victor, I'm going to ask you to address this next question, although, Ioana, you may want to add on because it's a really hot topic, and that is with respect to comorbidities. How do we consider comorbidities during this diagnosis, and what do we need to think about with respect to therapies, and maybe even some of the newer therapies, when we manage patients with pulmonary hypertension and comorbidities? Victor?

Dr. Moles:
Yeah, that's a great question. I think the way that I would answer that question is I would try to define 2 different patients that may look alike in the beginning. So one patient is a patient whose comorbidities is primarily driving their symptoms. So I'm thinking of a patient who's elder, who has CKD hypertension, diabetes, who, when I look at the echocardiogram, has a dilated left atrium with persistent atrial fibrillation, who looks volume overloaded and has orthopnea, compared to a patient who has predominantly pulmonary vascular disease but, on top of that, has comorbidities. So that may be a patient that it may be younger or elder, but the comorbidities are not so pronounced. A look at the echocardiogram on the left side of the heart is relatively preserved. Most of the abnormalities are located on the right side of the heart, with a dilation dysfunction of the right ventricle, changes in geometry, Doppler evidence of suggested elevated pulmonary vascular resistance.

So the first patient that I mentioned is the patient that I would probably optimize the comorbidities first and then reevaluate, then get an echocardiogram, then reassess their symptoms. Compared to the second patient, which is a patient that raises an alert, an alarm in my mind, and I want to investigate their degree of pulmonary vascular disease first, despite their comorbidities.

Just a couple mentions on sotatercept. There is data showing subgroup analyses on the sotatercept trials. The patients who have diabetes, hypertension, obesity, and coronary disease, they get the same degree of benefit from sotatercept compared to if they did not have any other comorbidities.

But I don't know, Val. What do you think?

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Dr. McLaughlin:
Yeah. No, Victor, I think that was a perfect answer. I think it goes back to getting the diagnosis correct. Is it someone predominantly with Group 2 pulmonary hypertension who maybe they're just well diuresed or their cath is done at 5:00 PM and they've been NPO all day and they kind of technically meet the criteria for PAH, but they're really Group 2, and you should treat that Group 2, as opposed to someone with really bad pulmonary vascular disease that just happens to have well-controlled systemic hypertension. So, yeah, I think you gave a perfect answer.

And I just want to maybe ask Ioana if she wants to comment on the pulmonary phenotype as well.

Dr. Preston:
Yeah. So the pulmonary phenotype that has been described by both the British group and the European group and databases highlights patients who have some degree of lung disease, maybe emphysema, but not significant enough to trigger a diagnosis of severe emphysema. However, they're significantly hypoxic, their DLCO, their gas exchange is very low, and they have significant pulmonary hypertension. And this is a subpopulation of what we call Group 1 PH with a pulmonary phenotype that is very reluctant to respond to the treatments that we have available for Group 1. I think they have to be studied in a multidisciplinary fashion and evaluated for lung transplant soon because these patients have a very poor outcome, and they don't respond to the therapies that we have available.

Dr. McLaughlin:
Yeah. I think that was a great summary.

Victor, I'd like you to address this next question. You're a cardiologist, you do the right heart caths in our patients, and you're very meticulous with getting wedge pressures and knowing the patients going in. Now, we talk about the hemodynamic definition. It uses a cut-off wedge of 15. But 15 is not really a normal wedge, right? Really, a normal wedge is 12. And on the other hand, there are patients with bad pulmonary hypertension who have interventricular interactions, who really have a PVR of 12 with the wedge of 18, and it really is pulmonary arterial hypertension. And so at the last World Symposium, this concept of the zone of uncertainty of a wedge of 12 to 18 was discussed. And, Victor, I think I just would like to ask you, how do you put that in perspective? What recommendations do you give to the audience about that uncertainty?

Dr. Moles:
Yeah, so, Val, this is a great question. I don't think that there are great answers. But I think the way that we should always approach the wedge measurement is we need to be meticulous. The first thing, if you are doing the right heart catheterizations or you're working with somebody who's doing the right heart catheterizations, know your patients first. So look at the echocardiograms, understand the pretest probability for what that wedge should be kind of going into the right heart catheterization. The second thing that I'll say is, always zero. That's the most important part of a right heart catheterization. It has to be done before it, you start your procedure. It has to be done always the same way. And you can have a beautiful procedure with beautiful waveforms, but if you didn't zero correctly, your wedge may be falsely high or falsely low. And then, other things that you can do, being always very cautious and meticulous under fluoroscopy as if you're not sure if your wedge tracing is accurate. Deflate the balloon, under fluoroscopy slowly inflate the balloon, looking at your tracing until you get that wedge tracing. And the other thing that we can do is just get a wedge saturation, and that wedge saturation should be very close to what the systemic saturation is looking like.

So I think that the best way to dealing with wedge pressure is to get an accurate wedge pressure. But then, again, we have to put everything into context. Pulmonary hypertension is not a disease of right heart catheterization versus other things. It's a clinical diagnosis and we need to put in the patient information, we need to look at the echocardiogram, we need to look at the hemodynamics and put them together. As you said, there are patients who have very advanced hemodynamics who they may have been particular interdependence or their wedge pressure may be high because of their severe pulmonary vascular disease.

Dr. McLaughlin:
That was a great summary. I think the other thing I would add to that is that if the patient had a lot of risk factors for diastolic dysfunction going in and you get a wedge of 12, maybe you want to do a fluid challenge and see if that really is the diagnosis. So I think there's certainly a lot to think about.

We're almost at the top of the hour, but I want Ioana to just very quickly answer this last question because it's a – and sorry, there's not a quick answer to this, Ioana, but it is a question that we're getting asked more and more. Would you consider deescalating prostacyclin analogues in patients doing well on ASIs, and how would you approach that?

Dr. Preston:
Very cautiously. Having experience with deescalating with other compounds and other drugs that we've had available, I would only consider in patients who have almost normal hemodynamics, functional class I, and the right ventricle and right heart looks, I would say,

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fabulous on the echocardiogram, and my cardiologist is like giving 2 thumbs up. Other than that, I will be really cautious until we get more data and more information.

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