Roundtable Discussion: Highlights From the Seventh World Symposium on Pulmonary Hypertension

Rachel Hopper, MD, Sandeep Sahay, MD, MSc, Scott Visovatti, MD, and Lori Reed, MSN, APRN, FNP-C met to discuss the Proceedings of the Seventh World Symposium on Pulmonary Hypertension, which were recently published in the *European Respiratory Journal* (Humbert et al. *Eur Respir J*. 2024;64(4):2401222). The key takeaway from this discussion was to highlight the inclusion of a fourth pathway drug (activin signaling inhibitor) in the treatment algorithm. The panelists also explored the implications of the changes in the classification of Group 3 PH, the importance of phenotyping patients and the potential for a "zone of uncertainty" in the classification of patients. Lastly, they discussed the implementation of genetic testing recommendations, the continuum approach to patient treatment, and the complexities of diagnosing and treating PH, particularly in relation to chronic thromboembolic disease.

Dr Hopper: I'm curious, for all of you who take care of adults, what you think were the biggest changes and most impactful recommendations from the World Symposium that were shared at conference this year.

Dr Sahay: For me, the biggest takeaway was the inclusion of the new pathway drug, which is an activin signaling inhibitor, in the treatment algorithm. I think this World Symposium document highlights where we can use it in the treatment algorithm. The other change, big change, was to suggest not high risk and high-risk categories at baseline. Probably an attempt to simplify it. But it also had a box created along with it which had a lot of information to be paid attention to when you're performing risk stratification in PH patients. So I think this was a little different approach. But I guess the biggest takeaway for me still is the introduction of the fourth pathway drug in the treatment algorithm.

Lori Reed: Yeah, I'll kind of copy you in that it gave us some guidelines in adding in this new fourth-line treatment, which is helpful. We weren't part of the study, but we're definitely using enough of it in the right population, and so to have that to guide us is helpful. It also gives me a little bit of a pause to see where they place it. You know, that's kind of interesting because, in our practice, the 3 foundational pathways we're very familiar with, and we're pretty heavy handed with our parenteral prostacyclins in the patients that really need it. And so to see this newer activin signaling inhibitor placed potentially prior to that is very interesting. One thing that they really stressed in the World Symposium that I think is valuable is patient-centered care, the patient's perspective, the patient's experience, and making sure that that's wrapped in, in every step of their PH journey, and so having them part of the symposium and part of every journey of it, I think, was one of their key points, and they made that clear, and I appreciated that.

Dr Sahay: She's absolutely right. This World Symposium probably was the first one to start with the Patient Perspective Task Force to highlight how central patients' viewpoint or opinions or expectations are in the management of PH, so I think that was a very nice and a very welcoming move. We have patients that presented and also participated as authors in these documents. I think that's unique. Thanks, Lori, for bringing that up.

Dr Visovatti: The European guidelines had prepared us for the idea of comorbidities. Instead of thinking about clear-cut Group 1 PAH versus Group 2 PH versus Group 3 PH, we need to consider the possibility that Group 1 PAH may coexists with some degree of parenchymal lung disease or left heart disease. This brings up many of the challenges we face in our daily clinical PH practice. Is what appears to be a comorbidity actually the primary driver of the disease? Do we need to modify how we treat patients who appear have Group 1 PAH but also have COPD? It's important to think about patients' comorbidities as being on a continuum; this was really well presented at World Symposium.

Dr Hopper: That's a great point. I'm curious: in your practice, how much impact did the change of the structure of Group 3 diagnoses going sort of from a physiologic diagnosis to more of a clinical diagnosis, what impact do you think that will have on the care of patients with Group 3 PH, or even patients with Group 1 who also may have lung disease?

Dr Visovatti: That's a great question for the entire group. I think this is one of the most important questions to answer in all of PH, and it takes a multidisciplinary care team to answer it. I'm a cardiologist, so I really depend upon the expertise of the pulmonologists at our institution to help figure out if a patient has Group 1 PAH with some lung disease versus Group 3 PH. I think the Seventh World Symposium emphasized the importance of a multidisciplinary approach to help figure out PH diagnosis and treatment.

Lori Reed: I work in pulmonary. I also treat all advanced lung disease including interstitial lung disease. Also, we get our COPD patients, and from my perspective, this currently won't change much of what I do, but I think it's setting us up to help with phenotyping in the future

and research designs and trials, so that we can start to build on what is going to be most successful for the patients with this phenotype or that phenotype. I think they're setting us up for what we need to do next.

Dr Sahay: Yeah, I think it's just the evolution of what we used to call just Group 3 pulmonary hypertension. Now we have different phenotypes, and we actually have successful treatment for one of the groups. I think this really highlights that Group 3 PH is not just the same disease in all. Going to what Lori just mentioned, about the importance to phenotyping them, and then selecting treatment, in Group 1, we have different types of PH—idiopathic, heritable, calcium channel, connective tissue disease, etc, but our treatments work on all of them, but Group 3 PH is way more heterogenous. You cannot treat them in the same way as you do it for Group 1 PH. Initially, we used to think of only Group 3 or PH due to diffuse parenchymal lung disease. Now you have PH-ILD, COPD-PH, combined pulmonary fibrosis, and emphysema, a lung phenotype PH which is still not very clearly defined, so within each group, there is evolution of the classification. The difference between Group 3 and 1 PH is that, in most of the Group 1 PH, drugs work for most of that group's subtypes of PH. But we have not achieved that level of success in Group 3 PH as yet. But the first thing is to identify that these are different entities, and hopefully, by the next World Symposium, we might have more successful therapies which may be working for all subtypes of Group 3, but we don't know yet. But I think it's really important to categorize patients correctly.

Dr Hopper: And another discussion that I found really fascinating was in regard to Group 2 and the importance of the wedge pressure in hemodynamics. Seems like there were some strong opinions expressed by people in the audience, as well as the speakers, in terms of the appropriate wedge cutoff and some of the pitfalls of obtaining an accurate wedge. You know, as a pediatrician, the cutoff of 15 has always seemed wildly high to me. A wedge pressure of 15 is almost never normal in a child. I thought the discussion was interesting, and I'm curious if you think that sort of "zone of uncertainty" that was described may make that idea of overlap and recognizing that diagnostic heterogeneity will be improved with recognition that there is a zone. It's not necessarily an absolute cutoff of 15. There may be some wiggle room, either due to the patient's intrinsic, clinical state, or unfortunately, the errors in measurement that can happen.

Dr Sahay: I think that goes back to the original question of phenotyping these patients. We all know that, in the REVEAL registry, when it first started, it had wedge up to 18. They actually published separately the outcomes in patients between the wedge pressures of 16 to 18 and 12 to 15. It did show that higher the wedge at follow-up in these patients did not carry much worse outcome. It's important. As far as the hemodynamic definition is concerned, I personally feel that staying at 15 is reasonable, but I agree that wedge pressure of 12 is normal. With that, I have a question for you, Rachel. What about the classification in pediatric PH which they propose? What are your thoughts on that?

Dr Hopper: The Pediatric Task Force recommended continuing the definition of pediatric PH with an indexed PVR of >3, which I think is reasonable because we do index for body surface area. For me, I think the interesting thing was thinking about treatment algorithms in pediatrics because this was the first time where they really separated out congenital heart disease with open shunts versus other PAH, and a bit of discussion about our kids with developmental lung diseases, but I think we're again recognizing the idea of different phenotypes in pediatrics that may need a different approach to therapy. That said, we don't have enough data in children to make evidence-based recommendations. And yet the Task Force recommended upfront dual therapy in children extrapolating from adult data. They mirrored the adult recommendations, which was interesting. And I think many of us who care for kids with PH have adopted that approach over the years after the AMBITION trial. I thought it was interesting that they did incorporate that this year as the concrete recommendation. And like always, it highlights that we have to do better in terms of getting data on kids and how these medications are used in children.

Dr Visovatti: As we discuss the hemodynamic criteria for PH and the need to more deeply phenotype children and adults with PH, we should emphasize the need for accurate hemodynamic assessments. Also, as a long-time believer of exercise PH and the value of provocative testing, I was excited to see that the Proceedings include some great discussion about pre- and postcapillary exercise PH, which are now defined by pressure versus cardiac output relationships. I'm excited that the global PH community recognizes the importance of gathering accurate hemodynamic information to facilitate deeper phenotyping of PH. This is really what's going to take us to that next level in terms of enrolling appropriate patients in clinical trials. How do we include the right patients? What inclusion and exclusion criteria should we use?

Dr Hopper: That's a great point, Scott. One of the other task forces that wasn't explicitly presented, but was reviewed in the guidelines, was the Genetics Task Force. Along the lines of phenotyping, there's been a big interest in the genetic phenotyping of our patients to understand that better. The recommendation of the Task Force was that all Group 1 PH patients should be tested, and children with Group 3 developmental lung disease PH should have genetic testing done, which I think in a perfect world would be amazing, but there are a number of challenges in terms of having adequate genetic counseling support and getting genetic testing paid for. So I'm curious to hear from the adult providers. We have some workarounds in pediatrics, but do you think that will be something that you can and will implement in your practice, or do you perceive

challenges with implementing that piece of the recommendations?

Dr Sahay: No, I think, personally speaking, I am always looking forward to recommendations from genetic testing in PH because we do it routinely in our clinical practice. I really liked the table in the Genetics Task Force manuscript, then if the target gene testing is negative, then how you move on to do the whole exome sequencing. I think that's a very nice recommendation and just highlights the importance of performing genetic testing in PH care. I think genetic testing is an issue, not just with the cost but also an awareness among the clinicians. So the more we put it in the guidelines and recommendations like World Symposium, the more it will be acknowledged and people will be aware of doing it.

Lori Reed: We probably don't test enough in our center, but we don't have a lot of access to genetic testing and counselors, and our patients can't afford the extra costs of travel, so it would be a pretty big hurdle for us to even get a portion of our patients in with a genetic counselor at all. But I do agree, too, the more we use it, the more we recommend it, the more we keep it top of mind and push insurance companies and centers to hire more people and cover the costs that we'll get there.

Dr Hopper: Yeah, and we hope recommendations will help with that to give us evidence to go back to insurance companies and say, "Look, it's recommended."

Dr Visovatti: I'll add the importance of not only performing the genetic testing but sharing the information on a global scale. How often do we get a variant of unknown significance, and we don't know what to do with it? We need to share data in order to advance research efforts in this area. It's critical.

Dr Hopper: Good point. Absolutely.

Dr Visovatti: I also appreciate the emphasis on wearables. How often do our patients say, "My Apple Watch showed this today; what does it mean?" This is a hot topic.

Dr Hopper: Yeah, I think that's really exciting. There are even some studies of wearables in children as young as 1 year old, which is great, and as you mentioned, it's really exciting when we think about trials to have endpoints that are really meaningful to our patients. It'll be nice to see that included going forward and to see how that evolves.

Dr Visovatti: How does that work in a baby?

Dr Hopper: There are different types of actigraphy devices. This is a little bit tangential, but we can look at different parameters in terms of movement and heart rate variability. And these can actually be used in pretty young kids. Obviously, it's not a step count. That's not as useful in younger kids. But there are some indices that are useful.

Dr Sahay: The other important thing in this World Symposium was the Imaging Task Force. I guess this was the first time they had a task force to really talk about how imaging can improve diagnosis management. They discussed functional respiratory imaging. They also talked about standardization of cardiac MRI parameters. We have seen a lot of literature about MRI, and things have shown different findings depending on the data from different centers. It is more like a call to action that we should standardize the imaging parameters across the globe and see how we can best utilize those.

Dr Visovatti: Also, the emphasis on leveraging advanced imaging techniques when it comes to risk stratification. We intuitively know that we have to figure out how to include aspects of RV function in our risk stratification at baseline and frequent reassessments.

Dr Sahay: Was there anything groundbreaking in CTEPH? I guess we can say that, for CTEPH, instead of thinking that patient just needs surgery or is nonsurgical, it is more like a continuum approach. Now you may have a patient who will need surgery and may very well need BPA to complement to achieve full benefit. The RACE trial findings were discussed where they used a PVR of 4. It's just to highlight that, for a particular patient, you may utilize all the options: surgery followed by BPA, maybe medical therapy also.

Dr Hopper: I remember going to conferences in years past, and there were debates. It was surgery versus catheter-based, and it was one or the other. It's a great point to highlight now. I think there's a recognition of being able to incorporate different treatments, but I have to defer to you all because we don't see much of this in my world.

Dr Sahay: Right? And the one other point which we did not talk about when we were talking about Group 3 specifically was the PVR cutoff because abnormal with the new hemodynamic definition is at 2; however, INCREASE trial results included patients above 3 WU, and the World Symposium document said above 4. There was no clear recommendation between 2 to 3. It's up to the clinician to see how they want to approach between that range.

Dr Visovatti: Yes, that brings up the concept of "early PH." We need more clinical trials to help us figure out how, or whether, to treat patients with a PVR between 2 and 3.

Dr Sahay: I guess before this World Symposium and before the success of INCREASE trial, the European data showed that with a PVR of 5 WU have treatment benefit in this group. Then they talked about the post hoc analysis of the INCREASE data where they saw that forest plot with cutoff of 4 WU and more benefit in patients with PVR > 4 UW versus those with <4 WU. But I was thinking when the inclusion criteria of the INCREASE trial was mean PAP > 25 with PVR of 3 and above, then why are we making recommendations based on the post hoc analysis and not just what the inclusion criteria of the INCREASE trial was. I was just a little confused why we relied so much on the post hoc analysis data to make that

recommendation because it would have cleaned up this confusion between the PVR of 2 to 4 WU. Hopefully, we have more data to support it after the next World Symposium.

Dr Visovatti: Sandeep, I wanted to circle back to your very important point about CTEPH. If we use our new hemodynamic definition of precapillary pulmonary hypertension, then a large portion of the group of patients that we used to call "chronic thromboembolic disease" has now been reclassified as CTEPH. But should we really consider sending a patient with a PVR between 2 and 3 for endarterectomy? I think not. Also, patients with a mean PA pressure <25 mmHg were not included in the CHEST-1 trial, so we shouldn't be treating them with riociguat. These issues emphasize the need for more research in CTEPH. I think invasive cardiopulmonary exercise testing can help us figure out who really needs to be treated for CTEPH and in what way.

Dr Sahay: To me the answer lies in what your patient is telling you. If you have a patient with a PVR of 2.5 and you are seeing there is a lesion and the patient is saying that they're symptomatic and not able to do day-to-day activities, that's a situation where you need to do something. Now there could be another scenario where a patient was getting testing done for something else and you incidentally found CTEPH, but the patients says they feel fine and have no problems. The right heart looks fine, and well, that's a case you may do something or not do even if you identified it. In CTED patients, there is not very strong evidence that this really progresses to CTEPH. Then it's a big question if the patient is feeling fine: Should I do anything, or should I just observe the patient? That's a million-dollar question I guess we don't have the answer to right now.

Dr Hopper: Your comment takes it full circle to what we started with: Lori brought up the Patient Task Force, and I think keeping in mind that patient perspective is so important to incorporate into the clinical algorithms because, as you say, the hemodynamics are guidelines, but they're clearly not the whole story, and the patient perspective is so important in making decisions about treatment plans.

Lori Reed: What I was going to add a little bit to each one of these classifications is it's all coming back down to us better understanding the phenotype, better involving the patient, and understanding that this is complex, no matter which category they fall into. Remember to fall back onto your risk stratification that does include the patient's perspective and their functional class as well as the hemodynamics and everything else. Bringing it back together, treating the patient, meeting them where they are, and having our data and science helps support the group in which direction to go. And as Sandeep was talking about, you get a patient that you're unsure if it is something or if you need to do anything about it. I think the World Symposium is starting to help guide us with that, so that might be an opportunity to get the MRI or the CT scan and see the early changes, the early detection, and maybe get ahead on some of those patients where you think this was incidental.

Dr Hopper: That's a good point and a good way to wrap up here, incorporating all of that together. You tied it up nicely, Lori.