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Risk Assessment in Pulmonary Hypertension: Practice Trends and Updates

Announcer:
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Chapter 1

Dr. Bartoleme:
I'm going to start us out today talking about the definition, classification, and diagnosis of pulmonary hypertension.

To start with, there've be some changes to the definition of pulmonary hypertension over the last few years. At the last World Symposium, the mean PA pressure that defines pulmonary hypertension on a heart catheterization was lowered from 25 to 20, and that persists even with the recent updated World Symposium this summer. Also, the categories are similar in that precapillary pulmonary hypertension continues to describe patients with the precapillary disease in the small vessel pulmonary arteries, and hemodynamically in the cath lab, we define that, again, as the mean PA pressure greater than 20, a normal pulmonary artery wedge pressure or left ventricular and diastolic pressure, and then a pulmonary vascular resistance calculation, which helps us correct for cardiac output. Now, the PVR in the past have been greater than 3 Wood units, and it was recently lowered to greater than 2 Wood units, and I'll show you some data on why that is a little bit later.

There are patients, however, that present with combined disease, and you can see we also maintain that diagnosis as combined post- and precapillary pulmonary hypertension. Notice in that terminology, post comes before pre, which I have a problem with often when I say it because I want to say pre before post. But the reason that was specifically changed was because we wanted to emphasize that postcapillary pulmonary hypertension is often the predominant phenotype in these patients. And that's where there is an elevated pulmonary vascular resistance and mean PA pressure but also a higher wedge pressure.

And finally, exercise pulmonary hypertension is now back in the definition. It was many years ago. It was then taken out because the definition that we used in the past turned out not to necessarily be associated with a poor prognosis. However, some newer data in many kinds of pulmonary hypertension, including left heart disease-related pulmonary hypertension and also valvular disease-related and even some lung disease. Really, this data comes from the undifferentiated dyspnea workup has shown that when you take multiple measurements in the cath lab over time rather than just one and look at exercise and then slope that line with a mean PA pressure over cardiac output slope and get a value greater than 3 mmHg/L/min between rest and exercise, that that is associated with a poorer prognosis. And I’ll show you the data on that briefly here in a moment.

So if we look at mild pulmonary hypertension, and defining that here as anything between 20 and 25 on that mean pressure, and we look at population-based studies, and this particular one was done with the VA patients, many who had prevalent heart and lung disease. What we noticed is if we use a lower pulmonary vascular resistance at greater than 2.1 in this study, we captured 55% more at-

risk patients than our old definition of a PVR at 3.0. And in those patients, hazard ratio for mortality was 1.47. Also, they had increased hospitalization rates at 1.17.

Because a VA population, as you know, is mostly male, these results were then validated by Vanderbilt University in a sex-matched cohort and held up. There is no data for treatment affecting this risk, so this is a definition rather than showing that treatment affects it. But we can see here that even these mild levels of pulmonary hypertension in a population doesn't matter what it's from, and you can see we have those here by PVR on the bottom and their mortality hazard ratio on the y-axis. You can see if their wedge is low or if their wedge is high. They, again, had increased hazard ratio for mortality and hospitalizations, and you can see that in those 3 graphs there.

If we look at outcomes in patients who are referred to a pulmonary hypertension center with these mild levels of pulmonary hypertension, a really nice study was looked at out of the UK where they looked at their caths done between 2009 and 2017, and then they stratified them by hemodynamics. You can see that here in the top. So we can see in the red there's patients with a mean PA pressure less than 21 was 968 at the initial cath. The patients with a mean PA pressure 21 to 24, they had 689 patients in that cohort. And then, greater than 24, they had 1,272 patients, and those are stratified by PVR and diagnosis. If you look here on the graphs, what you're seeing on the one on your left side is survival probability on your y-axis and survival time-in-years on your x-axis, so up to 12.5 years there. So, long study. And you can see the tranches of PVR. So PVR greater than 3 Wood units, blue. The green line is PVR between 2 and 3, and your red, PVR less than 2 Wood units. And you can see survival time there, over years. And you can see it does differentiate itself nicely. And again, doing hemodynamics the other way, looking at mean PA pressure in those patients who had a PVR between 2 and 3, you can see it also gets differentiated in there by that mild PH hemodynamic. So mean PA pressure less than 21 in the red, and, again, green 21 to 24. And mean PA pressure greater than 24 in our traditional definition, they are blue.

And these findings were independent of age, sex, and whether they had heart or lung disease, and the majority of them did. If you look at that group in the middle with the mean PA pressure between 21 and 24 and a PVR between 2 and 3, 68% and 79% had heart or lung disease, respectively. So mortality is increased in this group no matter what their pulmonary hypertension is from.

What this tells us is that those people are important to study and look at, and they are defined as abnormal, so that's why they're in the definition. However, treatment recommendations are not there for that group. So all of our treatment trials are in people with a traditional definition of pulmonary hypertension, meaning 25 or above, and a higher PVR. So it's really important when using these definitions that when we use the right heart cath, we interpret it in the clinical context in our other testing to avoid misclassifying our patients, and also to avoid doing a right heart cath in the midst of an acute condition. This is a consult I do often in our institution where people are wanting to do hemodynamics when the patient is in the hospital for another reason, for example, a COPD exacerbation or other problem while they're in the hospital, and we universally tell them to wait until the patient is at the baseline.

Also, if you diurese a patient when they're in the hospital and then do their right heart catheterization, you may find hemodynamics that look like PAH when, really, the patient has left heart disease-related. So it's really important they be at their baseline. I show this ECHO here because it does have many findings of pulmonary hypertension. That D-shaped LV and the flat septum, middle pericardial effusion. But also, if you look at that LV, it's pretty thick, so this patient may have more than one problem going on or left heart disease-related PAH. A comprehensive and deliberate evaluation remains important.

Looking at exercise pulmonary hypertension, I already mentioned we're using that slope of the mean PA pressure over cardiac output line and that greater than 3 is defined as abnormal. It is associated with worse event-free survival in patients with chronic dyspnea, and that finding holds despite their underlying comorbidities. The definition is there, not to say we treat these patients, there is no data on that, but rather the definition allows for future study of this population.

Looking at the classification scheme of pulmonary hypertension, this was updated this summer at the 7th World Symposium and the changes are there in red, so just a few changes. I'll talk about the first one, which is calcium channel blocker responders on another slide. But you can see the other changes are, really, more differentiation between the left heart disease and, specifically, valvular heart disease folks. And then NPH associated with lung disease or hypoxia rather than having them all grouped together. There are very specific conditions there that are known to be associated with pulmonary hypertension. And finally, complex congenital heart disease in Group 5 pulmonary hypertension.

Talking about those long-term responders to calcium channel blockers. The term acute vasoresponder was removed from that classification, not because we don't want to do vasoresponsive testing, we do, but rather because this group was the only one not defined by pathophysiology but rather by an initial therapeutic strategy. And it includes patients who will both be long-term responders and those who won't and will progress to PAH. And so rather than being that specific diagnosis, it was changed over to being long-term calcium channel responders because these people do have a separate pathophysiology and prognosis. It does require long-term follow-up, so you really can't make this one on the initial catheterization, but you can test them for it and then follow them along. And if they

stay in that group, then call them long-term calcium channel blocker responders.

So also genetic abnormalities. There's a nice paper in there and have been several nice papers that talk about genetic abnormalities associated with heritable PH. BMPR2 is the one that's been described the longest and certainly often a board question on one's pulmonary boards. But there have been many more genes associated with pulmonary hypertension that have been discovered over the last few years. In fact, there are over 800 BMPR2 mutations alone, not counting all these other ones that you see on here. And it's becoming increasingly important that we test this, so we can really do genetic typing on our patients.

You also can categorize these into the function of the abnormality. So again, BMP/TGF-beta superfamily abnormalities include BMPR2, but also alkaline and endoglin, which is associated with HHT, BMP9, SMAD8, and caveolin-1. Ones associated with channels well described would be ATP13A3, and then the KCNK3 abnormality associated with interstitial lung diseases. Under transcription factors, we have EIF2AK4, and that one is associated with PVOD or PCH, and so important to test for that because it does indicate a poor prognosis and we may want to refer patients earlier if we find they have that. SOX17, associated with congenital heart disease, and TBX4, we'll discuss a little bit later.

So we want to do that counseling and then testing of genetic abnormalities in patients who have IPH, a family history of PH, even if it's not proven that they have a heritable in the past, anorexia-associated PH, and congenital heart disease. We always want to do that along with genetic counseling and, again, already discussed why we would want to do it for patients with suspected PVOD.

Also, there is a new algorithm published in the World Symposium papers this summer that really just simplifies the diagnostic algorithm for PAH, really, with steps 1 and 2 being things that can be done in a primary care office and then steps 3 through 5 more specialized testing. Just a couple of things emphasized on this are, to your left, if there is an alternative condition noted, you don't always have to proceed with invasive testing. If you know the patient has PH ILD or associated with other chronic lung diseases or diastolic heart failure and everything is consistent with that diagnosis, we can just treat that. And then on the right side, for those who you have a high suspicion early on in the workup, make sure and fast-track those with a high urgency so that patients' workups get completed in a timely manner.

Looking at echocardiographic measurements, both the European guidelines and our new World Symposium task forces have emphasized that we don't want to just look at pulmonary pressures, but rather all the things that we can see on an echo that are associated with pulmonary hypertension. Everything has a caveat, and you really need to look at all these things in their entirety, and here they are listed out.

Also in the World Symposium paper, there are images and what they look like, if you can pull those up, by standard views and what they might look like if they're abnormal. And, again, you can see the markings on here for things that are abnormal, whether we're looking at mid-systolic notch here in the RV outflow tract or looking at reduced RV fractional area change here between systole and diastole as shown on these images over to your right side.

On right heart catheterization, we need to make sure that's done carefully as always, but there's been a couple of nice papers talking about that wedge pressure between 12 and 18, and it has been defined as a zone of uncertainty. I really like that term, because 12 and below is really normal, and not 15 like we've defined it in the past. And so when I see a patient in clinic where the wedge is 13 or 14, that may be a person I want to do more provocative testing on, such as a volume challenge or some exercise to see if it's consistent with left heart disease pulmonary hypertension and really have a high index of suspicion for those patients.

So now, quickly, we'll talk about a patient case. This is a 15-year-old male patient we had a few years ago. He was born 3 and a half weeks premature and spent 6 days – so not long – in the NICU for lung problems but had struggled with dyspnea and fatigue with exercise since he was 9. He was diagnosed with asthma, but inhalers didn't help, and he had a CT scan of his chest done, which showed some air trapping. He had since developed chest pain that radiates to his left shoulder and decline in his exercise capacity that was bothering him at school. A TTE had been done already by the time he was referred, which showed right-to-left shunt through a patent foramen ovale. He had also, of note, been having problems with his knee and was asking to undergo knee surgery when we met him.

His past medical history is significant for ADHD, and he's treated for that, and he's a factor V Leiden heterozygote, which he had just known from a family member and been tested. On a social history, he's a teenager, he had smoked marijuana and a few cigarettes, and he is in high school. He had not taken any other stimulants other than that prescribed for his ADHD. And on family history, his biological father did have a PE and died at the age of 33.

High-risk CT chest was then done which showed mosaic attenuation bilaterally on the expiratory phase, but also some mild diffuse bronchial wall thickening and bronchiectasis and an enlarged main PA. Pulmonary function testing, you can see there, his DLCO is

normal. The rest of his testing falls within the normal range. NT-ProBNP was 58, and a cardiac MRI, and you can see that image right here, RVEDV was enlarged at 219 mL, but his RVEF is preserved, and stroke volume index, as you can see there. And then, here's his right heart catheterization. PA pressure mean was 52. His wedge is 9. You can see his output is there. QP and QS were done because we were looking at his shunt from earlier. PVR is actually very high at 18 Wood units. PA sat was 67% and he did not have a step-up on his sat run.

So he had genetic testing, and he was found to have a heterozygous frameshift mutation in exon 9 of the TBX4 gene. This is associated with childhood-onset PAH, small patella syndrome, so that explained his knee pain. And often with pulmonary parenchymal abnormalities that tend to be bronchial like they were in this patient, it's important to know not just because we can look for the pulmonary abnormalities and watch and treat those over time, but also looking at TBX4 mutations and time to death or lung transplantation in patients with PH. You can see time to death or lung transplantation is certainly accelerated, and this is the most common genetic abnormality seen in PH other than BMPR2.

Chapter 2

Dr. Franz:
I would like to talk about risk stratification in pulmonary arterial hypertension, and for this, why would we do this? Well, the bottom line is that we have drugs that can improve the hemodynamics in pulmonary arterial hypertension, but they have certain side effect profiles. We want to use enough medication to prevent progressive RV failure without using more medications than we need that may just add side effects and toxicity. And so we need to think about, once we have that diagnosis established, how should we treat it? And this is based on how we perceive the patient's risk.

So here is a patient of mine who is a 59-year-old woman who had mild shortness of breath when we first met. Interestingly, her grandmother died in childbirth in the 1930s, and 7 years ago her daughter actually underwent transplant for pulmonary arterial hypertension that was refractory to medical therapy.

So we think about screening siblings and children of patients with PAH; we don't necessarily think about screening parents. But sometimes the parents can show up later than the children with the diagnosis.

She does have a history of sleep apnea and rheumatoid arthritis that is treated with various medications in that regard. And so this is a situation where she could have familial pulmonary arterial hypertension or it may be related to her rheumatoid arthritis or both.

So on exam, her blood pressure is a little low at 102/80, and we know, in fact, that lower blood pressure is associated with a worse prognosis in pulmonary arterial hypertension. And her heart rate is just a little on the higher side at 87, and sometimes people are having an increase in heart rate in order to maintain total cardiac output even though their stroke volume may not be great. So it's important to think, is the heart rate 100 or is it 50, and that may have implications for how we interpret other things like our hemodynamics. BMI is just a little elevated at 31. Her jugular venous pressure looks normal, and she does have a prominent P2.

So she undergoes an echocardiogram that demonstrates an estimated RV systolic pressure of 65 mmHg, a D-shaped LV, like Dr. Bartolome showed you in those echo slides, with moderately enlarged RV with dysfunction, that's also moderate, and a normal inferior vena cava, which is another way to sort of look at venous filling pressure. The higher the venous filling pressure, the more we worry about RV failure. She also undergoes a cardiac MRI, and the RV ejection fraction is 41%. An important component of her evaluation is also pulmonary function tests looking for parenchymal lung disease or gas exchange abnormalities, and her diffusing capacity is a little low at 74% predicted, but with normal spirometry. Her 6-minute walk is relatively limited at 317 m. You or I might walk 600 m, and we know that 317 m is a relatively short distance. And we also measured natriuretic peptides, which are released by the heart in response to wall stress, and so they can be used as a marker of severity of heart failure, either left heart failure or right heart failure in the case of PAH, and you can either measure your brain natriuretic peptide or internal pro-brain natriuretic peptide; either one can be done. NT-pro circulates in levels that are 3 to 8 times higher than BNP, so we just have to keep that in mind. But her BNP is somewhat elevated at 280 pg/mL.

So she is further assessed in the cath lab, and it is noted her blood pressure is a little lower, heart rate a little generous. The right atrial pressure is 9, and so in you or me that should be less than 7. And so there's a little bit of elevation in the right atrial pressure suggesting that the right heart isn't that happy, but it's not 15 or 20 or really remarkably elevated. She does have severe elevation in the pulmonary artery pressure with the systolic of 72 and a mean of 44, and her wedge pressure is fully normal at 8.

She also has well-preserved cardiac index at 2.9 L/min/m^2. And so if we take that transformer gradient of 44 minus 8 and divide by the 4.8, we have a pulmonary vascular resistance of 9 Wood units. And so quite severe precapillary pulmonary hypertension. We measured pulmonary saturation, which is also associated with limitation in terms of cardiac output. And also, an important thing I like to do with my

hemodynamics is we might look at that index and say it's fine, and that should be prognostically reassuring, but it's partly at the expense of this heart rate being a little bit generous. So we can look at the stroke volume index by dividing that cardiac index by the heart rate. And the stroke volume index, how much that heart is pumping per beat index per body surface area is only 33, so she's actually fairly limited in terms of that stroke volume index.

She is given nitric oxide to look for evidence of response, and there's not really any substantial change with that, and so she's not an acute vasoresponder in terms of that definition. So we say her diagnosis is pulmonary arterial hypertension, either heritable or related to rheumatoid arthritis. She has a V/Q scan that shows no evidence of thromboembolic disease, and she also undergoes genetic testing and, in fact, turns out to have a BMPR2 variant that seems to explain the familial PAH.

So how are we going to treat her? Well, we need to understand her risk and so we do risk stratification, thinking about factors that impact outcome in PAH, and the key point about this is you do your baseline evaluation, then you're going to start treatment, but then it's critically important that you do serial 3- to 6-month interval reassessments in order to make sure you're really getting towards low risk, and if you're not, you should be augmenting your therapy. And this is a critical aspect of our longitudinal care of these patients.

So this shows the European Society of Cardiology and European Respiratory Society risk tools. And essentially, here you'll see that there are a set of clinical parameters that include signs of right heart failure, how rapidly they're progressing, has it been very gradual or very abrupt, and how much do they have in the way of symptoms in terms of functional class or syncope, which we find particularly worrisome. And so we think about those aspects, and we often think about exercise tolerance, and we can quantify that with a 6-minute walk where if that's over 440 m, we're quite reassured. If it’s under 165 m, that’s really worrisome. And she's sort of in the middle there. And we can also do cardiopulmonary exercise testing if we wish. A lot of people don't do that, but if we do, if you compare this to what you might see in left heart failure, the breakpoints are a little bit different, but essentially you have to be pretty severely impaired on your cardiopulmonary testing to have a big impact on risk.

We talked about the biomarkers here and she's sort of in the middle here in terms of intermediate risk. And the imaging aspect, and Dr. McLaughlin will get into this more in her segment, is a little bit limited in terms of risk stratification right now because a lot of the databases that created the risk stratification tools didn't have that much imaging data in them in order to inform this, so this information comes from various sources that includes some of the registries and additional publications. But essentially, we can look at how big the right atrium is. The bigger the right atrium, the more concerning. We can look at integrating the function of the right ventricle with metrics such as the tricuspid annular plane systolic excursion, how far that tricuspid valve is moving between diastole and systole, or other things like RV strain, and can integrate that with the pulmonary artery systolic pressure in terms of the afterload and can calculate these. And she's sort of in an intermediate zone here as well. We also can look at the MRI imaging. And we mentioned her stroke volume index was in the 30s, and that sort of intermediate risk here, even though her cardiac index was well preserved with that index that was greater than 2.5. But a little elevation of right atrial pressure and, again, the calculated stroke volume index in the cath lab was low at 31, so kind of in the intermediate-risk group here. One thing that all of the risk calculators have in common tends to be some assessment of functional class in terms of asymptomatic to class IV, 6-minute walk distance, and natriuretic peptides.

Another approach to risk stratification comes from the North American REVEAL Registry, which is a very robust way to risk stratify. And this includes variables that may be just intrinsic to a patient in terms of why they have PAH. So she has heritable PAH. The other risk calculators don't talk so much about that, so it's nothing we can change, but it's nice to be aware of it because that puts her at some increased risk, or if she had connective tissue disease it would do the same but maybe to a lesser extent. The other thing are demographics, like older men with PAH. Even though it's less common in men, older men don't tend to do as well, so that is a risk factor within the REVEAL registry as well. And REVEAL 2.0 also looked at hospitalizations, and so people that have been hospitalized in the last 6 months, that's an adverse factor. In addition, as in any kind of heart failure, if your kidneys aren't working well, that's a risk factor, and so this is incorporated into the REVEAL 2.0 calculator. And it also looks at heart rate and blood pressure. Again, nonspecific, but the higher the heart rate, the lower the blood pressure, the more concern you might have about the hemodynamic compensation of the patient. The 6-minute walk distance and the BNP values are in here, and if there's a pericardial effusion on echo, like Dr. Bartolome showed you, that suggests more adverse hemodynamics and so is a risk factor. Also incorporated in REVEAL is diffusing capacity for carbon monoxide. If you have a lot of gas exchange trouble, that may be a difficult thing to correct, and it is worth knowing about, and so it's an important thing to do.

Hemodynamically, if you have a markedly elevated right atrial pressure over 20 or a PVR less than 5, these are either adverse or favorable for prognosis and so we can total these up. And for this you add 6 so that you can get a positive number, and so the REVEAL 2.0 score is 10. The REVEAL Lite 2 score involves fewer variables: GFR, blood pressure, heart rate, functional class, 6-minute walk, and natriuretic peptides. And we sum those up and also add 6 and we get 8. So relatively high-risk situation by REVEAL.

And our patient is sort of in here, if we use the REVEAL 2.0 5-year curve, and so we can differentiate relatively low risk, less than 6 or

so, up to very high risk, sort of in this 10, 12, 13. And our patient is in here. So relatively high 1-year mortality if we were not to treat her at all.

The greater number of variables in REVEAL and REVEAL Lite may improve performance but doesn't prove that using them results in better patient outcome than using the other tools. It does account for these other patient-specific factors that we talked about and so I think it's very worthwhile to do this, especially when we first diagnose our patients. Some components, the calculators may be impacted by factors other than the severity of PAH. You could have a patient who doesn't walk very far because they're deconditioned, or maybe they're relatively obese and then their brain natriuretic peptide levels may be lower because it's partly lower in patients who have higher body mass index. And so when we're thinking about therapy, we're trying to improve the hemodynamics to prevent RV failure. We have to be sure that factors we are looking at as being adverse are actually potentially going to be modified by our hemodynamic therapies.

The noninvasive calculators are easier to obtain than those that include the hemodynamics, but hemodynamics are increasingly recognized to be a critical aspect of PAH, and we need to keep that in mind. In addition, the amount of imaging data that's in the REVEAL calculators and so forth is pretty limited because the databases didn't have so much, and so we're thinking more about incorporating echo and so forth.

So when we think about treatment, it's gotten simpler. If they're not high risk, they get a combination endothelin receptor blocker and PDE5 inhibitor. If they are high risk, they should get a parenteral prostanoid and ERA and a PDE5 and maybe some of these intermediate-highs should be treated that way as well.

And then we're going to reassess within a few months and try to work them towards low risk by either adding proteinoids, if they weren't on them, or adding an activin-signaling inhibitor such as sotatercept to their therapeutic program, which is a new aspect of our PH therapy recently.

Chapter 3

Dr. McLaughlin:

So this is data from the COMPERA registry, which has been validated in the French registry, and on the left, you see the baseline assessment, low, intermediate-low, intermediate-high, and high and how it impacts their prognosis. And then on the right, you see the assessment at first follow-up, how they change their risk score with therapy, and that has important prognostic implications as well. And some of this is why all the guidelines say try to treat to get them to the low-risk status. That's something that really impacts our approach to patients. But, Bob, as you said, there are limitations to these objective risk scores, and I'm going to pull out the 2 obvious ends of the spectrum to help describe this.

So one end of the spectrum, I describe these people as the folks who keep me awake at night. They're young patients who function pretty well and have low risk scores despite advanced hemodynamics and RV function. And the second end of the spectrum are those older patients who may have other comorbidities that impact some components of the risk score, and they function poorly despite mild pulmonary vascular disease. And I think it's those patients who are becoming more common in our clinics.

So let me tell you about one of my patients. I've been seeing her for a number of years now. She has IPAH. She was very sick at the time of diagnosis, and she's on triple therapy with intravenous epoprostenol at a dose of 44 ng/kg/min, tadalafil, and macitentan. Her last right heart cath is shown there. A mean PA of 81, PVR of 16.2, so really advanced hemodynamics. But despite this, she functions well. She says she can do anything she wants. Her hall walk is great; it's above 440, that magic number, which we can debate whether that's an appropriate number in a young person, but her hall walk is great at 617. Her BNP is normal. And when I do her objective risk scores, she falls into low risk by both the 4-strata and REVEAL Lite. But I showed you her hemodynamics there.

This was her echo the last time I saw her. That right ventricle gives me palpitations. Right? It's huge. It's dysfunctional. Her right atrium is big. And in the short axis view you can see how flat that septum is. It's almost invaginating during systole, reverse curvature. So even though this patient scores at low risk and the guidelines tell me I don't need to do anything else, I really worry about patients like this, and we all have them. They tend to be younger, without comorbidities.

Now, speaking of comorbidities, we are all seeing more patients with comorbidities in our practices. As the population ages, as the average age of the PAH patient goes up, we're seeing more comorbidities. And these are data from the REVEAL registry, which Bob already alluded to, that looks at the different comorbidities, and these are pretty frequent comorbidities in this registry, and the impact of these comorbidities on functional class and on hall walk. And those are 2 components of both of the noninvasive scores. So if you have comorbidities, you're more likely to have a worse functional class and a lower hall walk and, of course, your risk score is going to be worse. But is it because of the pulmonary vascular disease, or is it because of the comorbidities? Sometimes that's hard to tease out. And we think of the US as a highly comorbid population, and I personally think of France as, gosh, they have the cleanest registry of all,

but they're starting to see this more in France, too.

So these are data that were kindly provided to me by our colleague Olivier Sitbon, looking at the comorbidities in the French registry in the population that you think, oh, this is clear-cut PAH. 60% of them have at least one comorbidity, and you can see over 40% have hypertension; a fair number have diabetes and obesity even in the French population. And we know when you have more comorbidities, your outcomes are not as good.

These are data from COMPERA. On the left you see this very famous cluster analysis paper where cluster 1 was the clear-cut IPAH, was really only 12% of their population. And you can see, even though they have a diagnosis of IPAH, they do better than patients who are in cluster 2, which is the cardiovascular phenotype. It tended to be older women with hypertension and diabetes. And the worst group of all is those with the lung phenotype. So those are cluster 3 and tend to be male former smokers with a very low DLCO.

And on the right is a different analysis from COMPERA just looking at the number of comorbidities and the survival based on that. So the more comorbidities you have, the worse your outcomes are. And again, is it the pulmonary vascular disease, or is it the comorbidities, and how does this impact risk assessments scores and treatment goals?

So let me move to my next patient. She's a woman, 75. At this point she has scleroderma. I first met her in 2012, and she had relatively mild pulmonary vascular disease when we first met her, really due to the great screening that our scleroderma clinic has. And so her PVR was only 3.2. We treated her with PDE5 monotherapy, and she's been on PDE5 monotherapy ever since.

Her last right heart cath was a few years ago. PVR of 2.8, pretty well-controlled pulmonary vascular disease by all accounts. But when I last saw her in the office, she was still functional class III, her hall walk was suboptimal at 244 m, her BNP was high. And when you do the objective calculators on her, gosh, she's at intermediate-high risk by 4-strata, she's intermediate by REVEAL. The guidelines tell me I have to treat to low. I have to do something else. But really, what else can I do to help this patient?

Here's her echo. I showed you her last cath was from a number of years ago. Here's her echo, the apical 4 chamber. Her right ventricle is nice and normal, small. Remember, she was diagnosed over a decade ago, and as time goes by, she's probably aging a bit, probably is developing a little bit of a stiff heart, some HFpEF. You can see her left atrium is big in this image. And then you see the short axis view. Nice small crescent right ventricle around that left ventricle. The septum is moving with the left ventricle, exactly how it should be. And even though she is not meeting low risk, there's really no chance that additional PAH-specific therapy is going to help her. Her pulmonary hypertension is well controlled, and her age and her other comorbidities are contributing to the variables that make her risk score intermediate or intermediate-high.

And so that's why when we think about treatment decisions, there's so many things to think about, and, yes, objective risk scores are important. We should do them every time we see a patient in clinic. But there are so many other things to consider, and Bob already mentioned both hemodynamics and RV function on imaging are really complementary information to the risk scores. As the population ages, we need to think about the comorbidities, and of course, in any individual patient, you need to think about their goals, their quality of life, their support system, the route of delivery. Maybe there are some patients who are unable to manage some of the more complex medicines or don't have the social support to do that, and of course, all of these medications have side effects, so we need to balance the symptoms of the disease with the side effects of the medication.

So while objective risk scoring is great and we've done a lot of research over the years on this, and in our clinic we do a 4-strata and a REVEAL Lite 2 every time we see a patient, there are limitations to that, and some of the information should be complemented with other assessments of the pulmonary vascular disease such as imaging and hemodynamics.

Chapter 4

Dr. McLaughlin:
How do you differentiate between various types of pulmonary hypertension while maximizing interprofessional collaboration?

You know, Bob, you have a very unique PH clinic there at Mayo. You have both cardiologists and pulmonologists that work side by side, so maybe you should take the first crack at this one.

Dr. Frantz:
Yeah. Thanks so much, Val. That was a great presentation about PAH. So it's a couple of things. There's collaborating with our own professionals and other disciplines within our institution and also partnering with care providers closer to the patient's home in terms of the referral systems and joint management of patients. And so once patients come to us, if they turn out that on the PFTs and on imaging of the lungs, what I'll do is if the PFTs show a low DLCO, you should be doing a high-resolution CT chest, looking for evidence of parenchymal lung disease, and if you're starting to find that, if you're a cardiologist, then you need your pulmonologist to help you potentially guide understanding of that disease process because if they turn out to have Group 3 PH, then we have different treatments,

like inhaled treprostinil, and different decisions to make. And we know, for example, in Group 3 PH, the prognosis there can be very adverse and so maybe those patients need to be referred earlier for lung transplant consideration.

So the other thing has to do with finding these patients with thromboembolic PH, and the hemodynamics can look completely identical to Group 1 idiopathic pulmonary arterial hypertension, and the patient may not even have a history of DVT or pulmonary emboli. And so that's why it's so important to do VQ scanning. And if you find chronic thromboembolic findings, then you need to collaborate with teams or refer the patient to an institution that has expertise in chronic thromboembolic PH.

I would say that in terms of collaboration with professionals outside of my institution, I get phone calls regularly from providers in South Dakota or North Dakota or Iowa and places around where I am, saying, hey, can we talk about this patient together? Let's work through this. I'm not sure if this is PH, left heart disease. The wedge is kind of borderline. And then we might say, well, refer them down and we'll do some exercise hemodynamics and see if they really have more of a Group 2 phenotype. So I think that issue of helping people to understand when something is a little bit beyond their expertise, to send that patient on to a colleague or a referral center that has that expertise to be sure you've got the right diagnosis before you start treating.

Dr. McLaughlin:
Yeah, I think that's great. I guess I would also add a couple things in terms of interdisciplinary or interprofessionalism. Like, well, you have to work closely in some areas that might be good opportunities for screening. So what I alluded to, working closely with our rheumatologists so that we can make sure they're implementing screening programs and get the scleroderma patients early, or Sonja probably has a lot of experience working with the hepatologists and getting to some of the portal pulmonary patients in a timely fashion. So I think there's a tremendous amount of opportunity.

Sonja, do you want to add anything to that?

Dr. Bartolome:
Yeah, I agree with all that. And depending on where you're practicing, actually, probably anywhere you're practicing, I tell people, find a buddy to go. I have somebody in radiology and nuclear medicine and the cath lab. If you're not someone who's in the cath lab, having a person and then really developing that interest and having somebody to pick up the phone when you need those studies done, it really does take a team. And sometimes you just need to get that one person in a group that you know you can call and work with. But, yes, everything you-all two said also.

Dr. McLaughlin:
The next question has to do with use of PAH-specific therapies in comorbidities, and, Bob, you put up the algorithm from the 7th World Symposium. And I don't know that you called it out, but a major difference between that and the 2022 ERS/ESC guidelines is we no longer have that little step to the right where if there's comorbidities, only start one therapy at a time. And I think this was a topic of really important discussion at the World Symposium, and I think it actually starts with getting the diagnosis right. And, Sonja, you mentioned the zone of uncertainty, and I think there's a difference between a real and true PAH patient who happens to have hypertension and may be very well controlled and, really, one might treat that patient aggressively with double combination therapy as opposed to a patient who technically meets the hemodynamics of PAH but, like, in our hearts, we know that they don't, and I think that's where the zone of uncertainty comes into play here. You might see a 75-year-old woman with hypertension, diabetes, obesity. Someone has diuresed her really well. Or there's a STEMI and her cath is not till 5 o'clock and she hasn't had anything by mouth all day, and you get a wedge of 14 and a mean PA pressure of 26 and her PVR is 3.2. And you technically could call that patient PAH based on the hemodynamics, but that patient probably doesn't have PAH. That patient probably should have a volume challenge. So I think it starts with the diagnosis.

I don't know if either of you want to comment on, really, the importance of that diagnosis before making the treatment decisions of combination therapy or any certain therapy in patients with comorbidities?

Dr. Frantz:
Right. I just think it's incredibly important to get that diagnosis right in the first place, and that has to do a lot with thinking really carefully about whether the findings in the cath lab match what you expect when you send the patient. So you might have somebody that is a young woman, like the kind of patient that Dr. Bartolome presented with, with a PAH that's genetic, and they have a cath somewhere and the wedge is 20 and you realize there's no reason for that. The left heart is completely normal. The left atrium is normal size. And then it's critically important that you repeat that cath and prove that the wedge is actually normal so that you can treat them appropriately.

On the other hand, you might have a patient who has clear precapillary PH with pretty elevated PVR who happens to have some diabetes, sleep apnea, and obesity, and if they really have a Group 1 hemodynamic phenotype and just happen to have these comorbidities, they should respond quite well to your PH therapies. And if anything, I think that part of the change in the

recommendations from the World Symposium had to do with that risk that if they have a comorbidity and then you go with monotherapy, you may be undertreating them because the combination of a PDE5 and ERA drops PVR about 50%. It's pretty remarkable, really. So it's important to separate a comorbidity in a patient who clearly has Group 1 PAH from a patient who more has Group 2 issues and it doesn't really make sense to treat them in a Group 1 fashion.

Dr. McLaughlin:
Yeah, I think that was a nice summary. And then I would just add in terms of any specific therapy – this question actually was about selexipag – but these analyses have been done on many randomized controlled trials. So the patients who are clear Group 1 PAH and happen to have comorbidities, 1, 2, some even 3 comorbidities, they do tend to have the same treatment effect.

Sometimes they have a little bit more side effects, but there have been some analyses from AMBITION, from GRIPHON, from many studies that show that these patients with comorbidities do benefit. And of course, remember these trials usually require a PVR of greater than 5, so it's usually a real deal PH patient. It's not like that older patient with the PVR of 3.2 that I described.

Sonja, there's a question about early diagnosis. So in your practice, what do you do? How do you improve early diagnosis, and what's the biggest challenge?

Dr. Bartolome:
I think the biggest challenge is that the early symptoms of pulmonary hypertension, as we all know, are nebulous. They're dyspnea on exertion and fatigue, which nearly everyone has at some point in their lives. And so I think that's the challenge, finding them early. You just have to have a low index of suspicion in people who don't have a diagnosis that matches their symptoms. And so what I tell folks, and when I go talk to family medicine clinics and that sort of thing, is most things really are a diagnosis of COPD or heart failure or asthma. Most things are. But you should have matching pulmonary function tests or an echo that match that level of dyspnea for your patient. If you don't or I have asthma that's not responding to inhalers and I don't have pulmonary function testing, that's when you really need to pursue more of a workup. So that's our biggest challenge is the symptoms. But how do we promote that is really getting out and talking to people, and not just the people I interact with all the time, my cardiology colleagues and such, but rather those primary care folks and the people who are really the entry point into the system to really be on the lookout for unexplained dyspnea.

Dr. Frantz:
Yeah, I was just going to say that, and to Val's point about how good the rheumatologists are about screening for PAH, this is something we also need to push because finding those scleroderma patients early is really important. And I would just also briefly mention that AI ECG algorithms are coming along. It's basically taking the electronic signal of the ECG and analyzing that in a way that finds things that our human eyes cannot see that are associated with pulmonary hypertension. And so it may be, in the future, if a patient comes into a general medicine practice and has dyspnea, they get an AI ECG that may raise concern about pulmonary hypertension, or it may raise concern about left ventricular systolic dysfunction or amyloidosis, and then that tool will be an additional factor that we can use in understanding if they might have a disease such as pulmonary hypertension.

Dr. McLaughlin:
Yeah, I think that's a great addition, Bob. I was going to bring out, also, the opportunities we have for screening, like in patients with scleroderma or like in the liver disease patients or like in patients who have genetic mutations have a positive family history.

And along those lines, there is a question about genetic testing, and there was a whole taskforce on this at the World Symposium, so maybe, Sonja, you want to take this one: What role does genetic testing play in understanding and managing pulmonary hypertension, and how do you facilitate it in your practice?

Dr. Bartolome:
Yeah. I think Bob mentions in his talk also that genetic testing can really help us in quite a few ways. First off, in risk, heritable pulmonary hypertension we know has higher risk than some of the other types, and so I really want to know that for prognosticating. And if I'm leaning on the edge of adding additional therapy, that does go into my personal calculations when I'm deciding those things and risk scores and that sort of thing.

Additionally, as we mentioned, specific genetics have other comorbidities that go with them, so I might look for lung disease in, like my case, a teenager that I normally wouldn't look for it in. And so knowing that is really helpful. I think also, moving forward, I think the future is likely going to be genotyping and deep-phenotyping patients and then picking our therapies on the basis of that, and we can't do it until we start identifying what genes particular groups of patients have.

The good news is, it's easier than it's ever been. A few years ago it was recommended, but it was really difficult to get. Insurance wouldn't pay for it; it was very expensive. Now the way I facilitate it, I'm kind of lucky, as all of us on this talk are, in that I work at a place

that has a genetics department and I can just refer them. I refer them straight, they do genetic counseling and they do the testing, and insurance is paying for it almost all the time now if they're insured.

But the other ways I've gotten it done before is the patients can actually do it now because these companies do it and they'll pay money getting it done themselves. I don't like doing it that way because it doesn't come with genetic counseling. You're really going to have to explain the results. So if they aren't going to a geneticist for that, then you're going to need to do that for them because you're going to find all kinds of things when they do that. But those third-party companies are actually doing a really good job because I'll take my list of genes I want, and they're getting it all done. Though if you live close enough and can get that blood sent to an academic medical center with the geneticist, I recommend that first and foremost. But there are other ways.

Dr. McLaughlin:
Great. Thanks. That was a wonderful summary, Sonja.

Well, we're coming to the top of the hour, so I want to thank both of you, Sonja, Bob, great talks, really important information that you've shared. And I'd also like to thank the audience for joining us, and I hope you found this program useful. So thank you and have a great rest of the day.

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