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Pulmonary Hypertension: Comorbidities With PAH and Group 2 PH

Announcer:
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Chapter 1: Pulmonary Hypertension: Comorbidities With PAH and Group 2 PH

Dr. Maron:
I'll be speaking first on pulmonary hypertension comorbidities with pulmonary arterial hypertension and Group 2 PH.

The approach to pulmonary hypertension always begins with clinical acumen, which is based on physical examination findings, oftentimes echocardiography, which is the first quantitative test, driving decisions around the probability of pulmonary hypertension and, likewise, lung function. This is an important beginning starting point, since pulmonary hypertension often will fit into 1 of 5 general clinical groups: PAH, pulmonary hypertension associated with left heart disease, PH associated with lung disease, PH associated with pulmonary artery obstructions, oftentimes from thromboembolic causes, and then other forms of pulmonary hypertension that are likely multifactorial.

The initial point focuses on hemodynamics and the clinical profile, ultimately, to fit patients into one of these clinical groups. However, it should be important to note that after risk stratification and appropriate treatment decision-making has been made, clinicians must recognize that often in clinical practice there is overlap between patients belonging to more than one group. In fact, it is very common to encounter patients that have features suggestive of PH with left heart disease, as well as features with pulmonary arterial hypertension. This can create a bit of a diagnostic dilemma, which I'm here to talk about in more detail now.

So an early and accurate diagnosis of PH is quite important. It's tempting to rely solely on echocardiography. It's noninvasive, it's readily available, and it does give important information estimating pulmonary artery systolic pressure, as well as important information on right ventricular function, both of which are critical to staging and ultimately determining the best approach to patients with PH. However, echocardiography estimates of pulmonary artery pressure are oftentimes inaccurate, and information that is collected during right heart catheterization, in turn, provides a robust assessment of the hemodynamic profile of patients and ultimately is required to make an appropriate diagnosis of pulmonary hypertension, specifically, direct measurement of pulmonary artery pressure, the pulmonary artery wedge pressure, assessment of cardiac output, and these variables are taken together to inform the pulmonary vascular resistance are extremely important for diagnosing PH correctly.

As you can see from this figure, the relationship between pulmonary artery pressure, measured by catheterization, related to the estimated pulmonary artery pressure, measured by echocardiography, oftentimes varies substantially, and so ultimately, good clinical practice requires right heart catheterization to make the correct diagnosis of PH.

This figure shows the relationship between pulmonary artery pressure measured by right heart catheterization and all-cause mortality in

one national database. As you can see, there is a continuous relationship between these variables in which the classical definition of PH, which used a mean pulmonary arterial pressure threshold of 25 mmHg or greater, was associated with an increase in risk for mortality. However, information from this study also identified that patients with mean pulmonary artery pressure levels lower than that, beginning around 20 and to 24, were also at increased risk for mortality. This, in addition to other lines of information, helps to recalibrate understanding of the relationship between pulmonary artery pressure and all-cause mortality.

A similar observation was observed subsequent to this, focusing on pulmonary vascular resistance, in which information on the classic threshold of PVR 3 Wood units used to delineate pre- and postcapillary PH was refined to focus on PVR thresholds that were lower, in this study, emerging at around 2.0 Wood units, as important clinically.

Based on this information together in 2022 and then subsequently reaffirmed by the most recent World Symposium on pulmonary hypertension, the ESC/ERS PH guidelines restructured the hemodynamic criteria used to diagnose pulmonary hypertension. Those criteria are presented here in this table and focus first on patients with a mean pulmonary artery pressure greater than 20 mmHg, which is the sine qua non required to make the diagnosis of PH. Patients with precapillary PH also have a pulmonary artery wedge pressure equal to or less than 15 mmHg with a PVR of greater than 2 Wood units, and patients with isolated precapillary PH have an elevated pulmonary pressure and elevated pulmonary artery wedge pressure, but a PVR of equal to or less than 2 Wood units.

In 2022, a subgroup entitled combined pre- and postcapillary pulmonary hypertension was also acknowledged, defined here by mean pulmonary pressure greater than 20 mmHg, pulmonary wedge pressure of greater than 15 mmHg, but a PVR of greater than 2 Wood units, suggesting that there is intrinsic damage to the pulmonary vasculature, despite the fact that these patients oftentimes will have an elevated pulmonary artery wedge pressure and thus be at risk for pulmonary venous hypertension in addition to changes in the precapillary pulmonary vasculature.

It's important to recognize that in clinical practice, pulmonary artery wedge pressure, which is used to delineate patients with pre and postcapillary PH, is subject to interpretation and that interpretation is based on a number of considerations that are technical as well as situational based on the clinical circumstances. Performing a right heart catheterization with maximal accuracy oftentimes requires expertise in key steps to performing the procedure, including zeroing the catheter appropriately, ensuring that the measurements are captured without respect to dramatic changes that may occur throughout the respiratory cycle, particularly in patients with obstructive lung disease, the use of breath arrest maneuvers to prevent confounding variables such as lung disease from affecting the interpretation of the data, as well as some of the other parameters to consider as listed here on this slide.

This, overall, creates a conceptual framework in which there is a resulting zone of uncertainty in which patients with a pulmonary artery pressure between 12 and 15, possibly up to 18, should be interpreted based on the clinical circumstances, including information based on their clinical history, risk factors for left-sided heart disease, other parameters that might suggest a contribution of left heart disease as opposed to patients with pulmonary artery wedge pressure of less than 12 mmHg, which by definition is favoring an isolated precapillary pulmonary hypertension presentation.

As we'll discuss in just a few minutes, patients within this gray zone may be candidates for provocative maneuvers, including exercise or fluid challenge, to try to understand better the contribution of a stiff left ventricle or other features of the left heart to the overall pulmonary hypertension picture.

Timing of right heart catheterization is also important in the diagnosis of PH. Take the 2 following sequence of events in a patient who is 65 with hypertension and obesity referred for evaluation due to clinically evident progressive dyspnea. This patient, who is diuresed first to, say, a reduction of 5 kg of body water then referred for right heart catheterization, may result in the following hemodynamic profile in which pulmonary hypertension is present by virtue of elevated pulmonary artery pressure. There is evidence of precapillary contributions to this through a PVR of greater than 2 Wood units. But we see here that the pulmonary artery wedge pressure is 11 mmHg. Overall, meeting criteria for an isolated precapillary pulmonary hypertension diagnosis.

On the other hand, had the same patient been referred immediately for right heart catheterization, it’s possible that based on these risk factors for left heart disease, a different picture might have emerged, including one in which the pulmonary pressure and PVR are the same, but the wedge pressure substantially elevated, creating a picture that is more consistent with combined pre- and postcapillary pulmonary hypertension, which itself is associated with a completely different treatment algorithm. Thus, it's important to contextualize the results of a right heart catheterization based on timing and other clinical features.

This figure shows one potential approach to provoking left heart disease PH in patients who are referred for right heart catheterization or under consideration for right heart catheterization due to pulmonary hypertension. If the pretest probability of heart failure with preserved ejection fraction, for example, is intermediate, and there is evidence of right ventricular abnormalities on imaging such as echocardiography or ECG, a right heart catheterization may be recommended, whereas in patients with no evidence of RV

abnormalities, those patients can be considered for right heart catheterization in selected cases based on clinical burden of disease or other features that may raise the suspicion of an intrinsic pulmonary vascular disease problem.

For those who have a high pretest probability for PH with heart failure to preserve ejection fraction, it's important to remember that management of the underlying left heart disease is critical. In patients that have a referral at expert centers for right heart catheterization with a wedge pressure of over 15 mmHg but have a low probability for PH HFpEF, it is possible that consideration to left ventricular and diastolic pressure validation is indicated, giving the clinician a second datapoint to confirm the accuracy of the wedge pressure. And if those who have a high wedge pressure have an intermediate or high probability for HFpEF PH, then this is ultimately confirmed at the time of right heart cath. What's challenging, of course, is those patients with a borderline pulmonary wedge pressure between 13 and 15 mmHg. For those with an intermediate or high probability for HFpEF, then it's possible that provocative testing with exercise or fluid challenge may be helpful.

More recently, we've seen the emergence of different probability tests, such as the H2HFPEF and the HFA-PEFF scores, which take a combination of clinical variables to estimate the probability that a patient with PH has that problem due, in fact, to left heart disease comorbidities. Provocative testing may also be relevant, based on emerging data, even for patients with a wedge pressure of less than 13 if substantial and numerous risk factors for left heart disease are present.

This table shows one proposed model to think a little bit about how left heart disease risk factors may be present in your patients. So of course, obesity, systemic hypertension, diabetes, and coronary artery disease are classic left heart disease risk factors, which we know often are present in patients who are older in age but present to our clinics for referral or evaluation of pulmonary hypertension. Arrhythmia and peripheral arterial disease are also considered left heart disease risk factors, which should require consideration when thinking about how to classify patients with PH accurately.

This table proposes a gradient in the relationship between severity of these risk factors and the probability that they may be related to left heart disease in patients with PH, such that one proposed model suggests that those who have at least one mild-stage left heart disease comorbidity are at lower risk for having left heart disease PH, while those that have greater than one severe-stage left heart disease comorbidity are at much higher risk for having left heart disease PH. Intermediate groups are presented here, and overall, this is used really as a road map to understand how to contextualize the number of different comorbidities and risk factors for left heart disease that might be useful in understanding the likelihood that a patient with PH has a contribution of that problem from left heart disease.

We mentioned exercise is an important provocative test earlier, and although exercise testing is not standardized across all centers, invasive cardiopulmonary exercise testing, or invasive right heart catheterization testing, has been very helpful in understanding prognosis in patients with undifferentiated dyspnea and in whom a normal right heart cath result is observed at rest. In these patients, the ratio between mean pulmonary artery pressure and cardiac output changes over the course of exercise can be helpful for understanding prognosis and can also be helpful for classifying patients that are likely to have left heart disease PH. The parameters that we use to describe that really hinge on the ratio and the change in pulmonary artery wedge pressure as a function of cardiac output, such that a dramatic rise in wedge pressure relative to increases in cardiac output during exercise are much more consistent with left heart disease PH as compared to patients who have a ratio change in exercise between wedge pressure and cardiac output that is less than 2 mmHg/L/min.

These data show that there is a prognostic association between performance during exercise testing relative to the wedge pressure to cardiac output ratio and should be used here just as a guide to understand that exercise is useful not only for pointing a direction of diagnosis, but also understanding overall risk stratification in patients that have exercise intolerance and concern for pulmonary hypertension.

The stages of left heart disease can also be helpful for understanding how we contextualize and think about pulmonary hypertension as a function of severity. So this diagram, which I'll show in different steps, models after the ACC/AHA heart failure stage algorithm in which stage A represents patients that are at risk for left heart disease PH, stage B includes patients with evidence of structural heart disease, stage C includes patients that have symptomatic heart disease, and stage D includes patients with advanced and right heart-predominant clinical presentations.

And we can break this slide down in different sections, so that we see here the clinical characteristics of each stage, beginning first with risk factors and comorbidities, progressing towards hemodynamic evidence of congestion on right heart catheterization with left atrial hypertension and the emergence of heart failure symptoms, including WHO functional class I- and II-type symptoms, into more concerning and more advanced stages of disease with systemic congestion and functional class II and III, consistent with stage C, and then ultimately, evidence of end-organ injury, ascites, organ dysfunction representing the most severe form of the clinical characteristics.

And these overlay well with our anticipated changes in hemodynamics over the trajectory of these different stages of left heart disease

PH, which as you can see include a steady rise in pulmonary artery pressure that is paralleled by a steady rise in pulmonary vascular resistance. At very end-stage forms of left heart disease PH, cardiac output, in turn, begins to fall due to cardiac dysfunction related to loss of right ventricular pulmonary artery coupling, which is an end-stage phenomenon of severe remodeling in both the pulmonary venous and the pulmonary arterial vascular beds.

Potential therapeutic strategies really align mainly with clinical trial data, focusing on optimizing underlying disease. In this case, consideration of lifestyle modification, SGLT2i therapy, and GLP-1 agonists for those at risk who meet a guideline-directed medical therapy indication. Ultimately, patients with severe symptoms in the setting of left heart disease PH should be considered for clinical trial enrollment, since the use of pulmonary arterial hypertension-specific drugs is not indicated in patients with left heart disease PH and should not be used regularly for that reason.

In summary, the hemodynamic definition for PH has changed recently to include patients with mean pulmonary artery pressure greater than 20 mmHg and PVR greater than 2 Wood units, which aims to emphasize early-stage diagnosis. Delineating PAH from left heart disease PH can be challenging in clinical practice, but risk scores are available as well as the use of fluid challenge or exercise during right heart catheterization in selected patients. Although as mentioned, standardized protocols remain forthcoming.

It's important to remember that right heart catheterization results require consideration of comorbidities and volume status, particularly when the pulmonary artery pressure is in the zone of uncertainty, which is about 12 to 15 mmHg, and possibly up to 18 mmHg.

Chapter 2: Management of Left Heart Disease-Associated PH

Dr. Cascino:
So let's begin with the staging-based approach. So why are we talking about PH left heart disease, or why should we care? It matters because people with left heart disease who develop PH do worse.

Highlighting here 41,000 patients from the VA, in the slide that Dr. Maron showed us, many of whom have prevalent left heart disease, who were referred for right heart catheterization. Once people develop PH with an increased PVR above 2.2 for both precapillary and postcapillary PH, people do worse. Here, showing post capillary PH, we can see that hazard ratio increases as the PVR goes up. When we look at a cohort of patients with HFpEF, 244 from Olmsted County who had the possibility of PH based on echo, we see that for patients with an RVSP that's greater than 48, here in black, and less than 48, in red, we see that as RVSP goes up, there's a large association with mortality. Patients with an elevated RVSP had a 3-year mortality of 50%. This disease is absolutely devastating once it develops.

And so how does it develop? The pathophysiology of Group 2 PH all begins with an elevated left atrial pressure. This pressure then gets transmitted back from the left atrium to the pulmonary veins and artery. Most commonly, PH with left heart disease is just this passive transmission that you see. You get a high wedge pressure. That high wedge pressure results in a high mean PA pressure and a PVR that calculates to normal. As you get more to the right of this figure, you see patients that for some reason, a genetic susceptibility that makes them more susceptible to developing a pulmonary vasculopathy or some inflammatory milieu, you get this increase in left atrial pressure that results in congestion and then subsequently results in vasoconstriction and remodeling of both the arteries and the veins. And this eventually leads to right heart failure. The involvement of both the arteries and veins is really what differentiates it from Group 1 PH. These patients, for some reason, as I said, are developing more severe PH. Patients who have a mild increase in their wedge, in the range of 15 to 20 mmHg, but a mean PA pressure is of upwards of 40 to 60, with PVRs that are going to be much greater than 2 to 3, upwards of 5 to 7 in this combined pre- and postcapillary group. While we really don't have a good way right now to identify patients who will have this increase, by adopting the staging-based approach that we'll talk about, we can hopefully prevent the development of more severe PH.

So how can we prevent PH left heart disease? Let's begin with people with stage A PH of heart disease. These are people who are asymptomatic with normal hemodynamics but have some risk factors for the development of PH. All our patients require aggressive treatment of any risk factors. All patients should have lifestyle modifications, these are going include evidence-based nutrition, exercise interventions. While a full discussion of all the treatment options are beyond the scope of the talk today, I do want to make sure that we focus on addressing comorbidities early.

And in focusing on addressing comorbidities early, we can prevent the development of heart failure, specifically heart failure that would result in pulmonary hypertension. This is data from the SPRINT trial. Almost 10,000 patients with a systolic blood pressure of 130 or higher and some increased cardiovascular risk, but did not have diabetes. They were treated to a blood pressure target of less than 120 or target of less than 140. Those in the treatment arm had a 38% reduced hazard for heart failure development. We can prevent heart failure.

Similarly here, is an article from *Lancet*. It's a meta-analysis. SGLT2 inhibitors for diabetes, for patients with and without a history of heart failure. If we focus on the bottom here that's highlighted, looking at patients who do not have a history of heart failure, there is a 23% reduced hazard for cardiovascular death or hospitalizations with SGLT2s. Treating hypertension and treating diabetes with SGLT2 inhibitors prevents heart failure. Prevention of left heart disease PH by preventing the comorbidities that cause heart failure is critical.

For patients who develop stage B and stage C PH left heart disease, we start to have this increase in left atrial pressure that's occurring. We keep all of the prior recommendations, including a focus on lifestyle and risk factor modification. With the increasing body of evidence to treat heart failure across the spectrum of ejection fraction, we really need to optimize guideline-directed medical therapy or GDMT. This is going to mean quadruple therapy for patients with an ejection fraction that's less than 50%. If the EF is greater than 50%, patients should be treated with an SGLT2 inhibitor and a mineralocorticoid receptor antagonist. As patients become more advanced with stage C heart failure, additional inventions like hemodynamic monitoring, we will talk about, as well as enrollment in clinical trials should be considered.

We don't have a ton of evidence of the direct effects of GDMT on PH. One example that we do have is shown here. This is the EMBRACE-Heart Failure trial. It's a randomized, multicenter, double-blind placebo-controlled trial. Ninety-three patients who could have had any ejection fraction, the full spectrum of ejection fractions, who had an implanted pulmonary artery pressure sensor were randomized to empagliflozin or placebo. We're showing the mean PA pressure with placebo in red, empagliflozin in blue on the left. On the right here, we have the difference between empagliflozin and placebo over time and in terms of mean PA pressures. And we see the significant decrease in mean PA pressures that was independent of diuretics. And this increase that we do see, it happens within weeks.

If the disease does progress, ultimately, we will get right heart predominant heart disease with stage D pulmonary hypertension. Our hemodynamics here are the combined pre- and postcapillary pulmonary hypertension, which for some people, as we've discussed, becomes more severe. Here, the goal is really ensuring care at PH expert centers to prioritize care and clinical trials.

I, of course, have not been emphasizing PH-targeted therapies. And so we must discuss the elephant in the room. There are no FDA-approved therapies, FDA-approved PAH therapies, for PH left heart disease. Up top here, we see our typical postcapillary PH. You get this increase in left atrial pressure that leads to an increase in mean PA pressure. That's mean PA pressure that's passive. In the bottom figure, showing combined pre and postcapillary PH, there's this out-of-proportion increase that happens as a result of changes to arteries and veins. The medications that we use to dilate the arteries can further increase wedge pressure and result in pulmonary edema, and it's really this pulmonary edema that's the most feared complication.

I've highlighted here a very high-level look at outcomes from multiple clinical trials across the spectrum of PH drugs. PDE5 inhibitors previously had some promising results. We'll talk about some more recent data and highlight, really, how the trials have mixed results. Endothelin receptor antagonists, there's been multiple studies now with volume overload as the complication. Prostacyclin, the first trial in heart failure with reduced ejection fraction showed increased mortality.

And so this table is from the 2024 World Symposium and highlights some of the more recent trials. Study drugs here include levosimendan, riociguat, macitentan, tadalafil. And when we really look at the primary results, they're not very promising. As the header highlights, no large multicentered trials show benefit. Mostly concerning more recently is the PASSION trial. This is a phase 3 trial of tadalafil versus placebo. It planned to enroll 372 patients. This trial was stopped early due to disruption in the study drug and ended up enrolling 125 patients. These are patients who had combined pre- and postcapillary PH. There was no change in the primary endpoint. There was an increase in all-cause mortality without a difference in additional secondary endpoints. And so the totality of the evidence has reinforced the position that PAH medication should not be used in PH left heart disease.

And so while we see this increased mortality with PH left heart disease in the pre- and post-combined PH, we should not be using these medications routinely. And so the question becomes, how can we tailor a treatment strategy and particularly tailor a treatment strategy through disaggregation to treat PH left heart disease?

And so proposing using a stepwise approach to doing this. In step 1, we really need to make sure we have an accurate diagnosis of why someone had PH left heart disease. There are a lot of reasons why someone may feel short of breath. There are a lot of reasons why someone may develop PH. Historically, we broke up PH left heart disease into HFpEF, HFrEF, and valve disease. The reality is there have been massive improvements in the management of a variety of heart failure etiologies, including across the spectrum of ejection fractions. We have new therapies to target valve disease. We have targeted therapies to treat hypertrophic cardiomyopathy and amyloid. The list goes on and will continue to evolve. Whenever PH is diagnosed, we always need to ask why. More important than ever to make sure that we have the correct diagnosis to target our therapies. There are going to be unique, therapeutic approaches that can be targeted.

Once we have the diagnosis, we want to treat the underlying left heart disease. This is going to include valve disease by the valve guidelines, heart failure by the heart failure guidelines, hypertrophic cardiomyopathy by hypertrophic cardiomyopathy guidelines, and on and on. We now have evidence-based care for many of these disease processes. We need to make sure that we're using it.

We know that left atrial pressure is the primary driver of Group 2. Step 3 is to use diuretics to optimize volume status and lower that left atrial pressure. The best evidence that we have that this approach works is from LVADs, in which when we really lower the left atrial pressure by offloading the LV, PVR improved. This is a study of almost 16,000 patients from the STS Intermacs LVAD registry who had pre- and postcapillary hemodynamics. PVR decreases by 1.5 Wood units per month in the first 3 months after LVAD placement. Similarly, when we look at pulmonary artery pressure-guided therapies for heart failure, we have on the right here, a meta-analysis of almost 2,000 patients from randomized trials. We see consistent positive effects for reducing worsening heart failure and subsequent hospitalization. Decreasing left atrial pressure works.

There are also a variety of comorbidities that contribute to heart failure and ultimately to the development of PH. This is an often-cited figure from Sanjeev Shah looking at this multisystemic involvement in HFpEF. We see comorbidities like obesity, type 2 diabetes, hypertension, CKD. I've added aging and Afib. All of these can contribute to the development of PH and the nonspecific symptoms that people feel, like fatigue and shortness of breath. There is increasing evidence that all of these cardio metabolic diseases impact heart failure. By aggressively treating them, we can hope to improve outcomes for people.

We also need to holistically treat all of these cardiometabolic diseases. This is going to include exercise training. We're going to do heart failure education and chronic disease management programs.

We need to get people to their heart failure centers as well as PH centers to enroll in clinical trials. This is a common deadly disease. It is also an area of active investigation. Critical that we get these people into clinical trials and have the opportunity to be involved in research.

And then if all else fails, we can consider individualized strategies to palliate symptoms if there is severe precapillary PH. This strategy is in line with the most recent guidelines here from 2022. We need to optimize the treatment of underlying conditions. We need to consider an individualized approach if they are severe precapillary PH. Drugs approved for PH or not recommended. Class 3 recommendation, level of evidence A.

And so again, we've highlighted while PH left heart disease is associated with increased mortality, heart medication should not be used routinely. We need to ensure the accurate diagnosis of the etiology. We need to treat the underlying cause, optimize left atrial pressure, and enroll patients in clinical trials.

Chapter 3: Management of PAH With Comorbidities

Dr. McLaughlin:
So I take you back to the 2022 ERS/ESC guidelines, which both Tom and Brad have mentioned, and here's the treatment algorithm. And this is the first time ever that a treatment algorithm right at the top separated out patients based on whether or not they had cardiopulmonary comorbidities. And you see an algorithm on the left for patients without cardiopulmonary comorbidities that is very much in line with previous algorithms, but then on the right they say, actually somewhat nebulously, patients with cardiopulmonary comorbidities in all risk categories should receive initial monotherapy rather than more aggressive therapy. And this was something that I think was quite controversial and generated a lot of discussion in the US. And I personally have discussed a number of limitations of the way this was done.

Now, in reality, these days we are seeing patients with more comorbidities. Gone are the days, when I was Tom's age, when we got all 30-year-old women with no comorbidities and PVRs of 15, right? That's just not what our clinics are like anymore. So here are data from the REVEAL registry that look at patients enrolled in the US who either have no comorbidities or who have any one of a number of comorbidities. And on the left, you see that any of these comorbidities leads to patients presenting with more advanced functional class, than patients with no comorbidities. And on the right, you see patients with comorbidities having a lower hall walk than patients with no comorbidities. So this also confounds risk assessment, which is a whole other topic to discuss.

And comorbidities are increasingly common. And we understand in the US, there's an epidemic of obesity and diabetes, but this is data from France, and look at this. Even in France, the majority of patients, 60% of patients that they diagnosed with PAH have at least one comorbidity, which is pretty striking considering the population differences. So we're all seeing this more.

These are data from the COMPERA registry, which is a European registry, and it wasn't necessarily just PAH, it was patients treated with PAH therapy. And they did a cluster analysis of patients based on phenotypes. And so cluster 1 was a phenotype that was really very much like the classic PAH. It tended to be younger, mean age of 45, no comorbidities, female predominance. That's really what we

might call very typical PAH. Cluster 2 was what we might call the cardiometabolic phenotype. These were older individuals, the majority with cardiovascular comorbidities, primarily women, a lot of atrial fibrillation as well. And then cluster 3 was really more of a pulmonary phenotype. It tended to be older men who had a history of smoking and a very low DLCO. So this is what we're all facing in clinic. We all see this in the real world.

And you can see from these COMPERA analyses on the left, looking at the phenotypes, cluster 1 being the more clean PAH phenotype in red, having a better survival than the cardiometabolic in green, and the cardiopulmonary in blue. And on the right is another paper that just looked at survival by comorbidities. And the more comorbidities you have, the worse you do.

So Brad showed this slide, and I think it's so important because sometimes it's hard to tell what is Group 1 PAH with a comorbidity and what is really left heart disease or lung disease or another type of PH. And I won't go through this in any detail because Brad does such a lovely job. But the point is that there is more to the wedge pressure than just the wedge pressure. It needs to be taken into the context of the patient's history and other clinical data, particularly the echocardiogram.

Now, what about the use of PH therapies in patients with comorbidities? The ERS/ESC guidelines would have us say, oh, if you have a comorbidity, you should get much more gingerly treatment. They should only start with one therapy. Well, the comorbidity discussion goes back a number of years. It really started when we were doing the AMBITION study. And the AMBITION study was looking at newly diagnosed PAH patients who were being randomized to receive either an ERA, ambrisentan, or a PDE5, tadalafil, or both together. And we were looking at the patients being enrolled, and we found that a large number of patients being enrolled had a lot of comorbidities, and we started to get nervous that the trial wasn't really a trial of what we intended as Group 1 PAH. So there was an amendment in the AMBITION study that excluded patients if they had 3 or more risk factors for left heart disease, that you could see on the bottom right, and also tightened up some of the hemodynamic criteria, requiring a higher PVR based on the wedge pressure. So there were about 100 patients enrolled who would have been excluded with the amendments that were taken out, what we call the ex-primary analysis set, and it's a smaller population, but you can see in that population there was a trend, but perhaps a little bit more benefit of combination therapy than monotherapy in that group, but nowhere near as striking as the overall study.

This has also been done in other studies post hoc. And this is from the GRIPHON study. Really the largest trial we've ever had in PAH that looked at the addition of selexipag to conventional therapy, ERAs, PDE5s, SGCs, in patients with PAH. And the primary endpoint was an event-driven time to event, morbidity/mortality event. And this was a post hoc analysis that looked at the patients with comorbidities who were enrolled. And you can see on the bottom right there, that there was a treatment effect in patients who had no, 1, 2, or a small number of patients had 3, so those are wide confidence intervals. But you can see that there was a treatment effect despite comorbidities. So in this population, who was clearly PAH, who happened to have comorbidities, there was still a treatment effect. So I think it gets a little dicey at times about what to do with these patients.

What we do know from both AMBITION and GRIPHON is that patients who have a lot of CV comorbidities tend to have more adverse events and higher rates of discontinuation of drugs. So that is certainly something that we need to monitor.

So Brad kind of went through this, but I'm going to give you an example of a few different patients, and these are patients like Tom and Brad and I and you see in clinic all the time. And so what are they? What really is their diagnosis? So I have it on a summary table, here. We don't have enough time to go through each case in detail. But on the left, you see Emma. She's 53. She has a family history of heritable PAH, so we're really worried that she has PAH. She's got hypertension, so she's got a comorbidity, but it's mild and well controlled. She presents with 6 months of dyspnea, has severe right ventricular enlargement, and moderate right ventricular dysfunction with an estimated RVSP on our echo of 85, and a PVR of 10. So I would say Emma is true Group 1 PAH. She has a comorbidity, but you have to look at the severity and number of comorbidities versus the severity of the pulmonary vascular disease. And I would not hesitate to treat Emma aggressively with combination therapy.

Then in the middle, you have Bess. She's 68. She has obesity, diabetes and hypertension. She's had dyspnea for a year. She has mild right ventricular enlargement and dysfunction on her echocardiogram. Her PVR is 5.2. Her wedge is 14. Brad might have already explained that maybe this patient should get a fluid bolus in the lab. But she's kind of one of these patients who might have qualified for a clinical trial. Her PVR is greater than 5, but she has comorbidities. And so is she Group 1 PAH? Is she PAH with comorbidities? This perhaps is the patient that we have to watch very carefully. I think she should be treated aggressively, but she may have side effects that we need to monitor.

And then on the right is Janet. She's 75. Also, obesity, diabetes, hypertension, a 2-year history of dyspnea. She has mild right ventricular enlargement but normal right ventricular function. Left atrial enlargement on the echo. Her cath, so her wedge pressure is 15. Her PVR is 3.3. She technically meets the criteria for precapillary pulmonary hypertension, but if you would have been really thoughtful, looked at her pretest probability, done an H2FPEF score, you might say, gosh, I'm really concerned about diastolic heart failure, about Group 2

pulmonary hypertension, given her a fluid challenge. And this is the type of patient who I would say, even though technically she meets PAH hemodynamic criteria, I don't really think she has PAH. I would send her to Tom and have Tom optimize everything else that he was talking about before even thinking about PH therapy.

So it's complex. There's a lot to the diagnosis here. When we are thinking about comorbidities in the setting of PAH, we need to balance. We need to look how severe the PAH is and how many and how severe the comorbidities are. If you have someone with really bad PAH and just 1 or 2 well-controlled comorbidities, that's much different than having someone with really a mildly elevated PVR and normal RV function and lots of comorbidities. So this can be a really tricky situation.

In this slide, we see kind of the spectrum. This is one of the challenges. There's not lines we can draw in some of these instances. On the left, you see the very clear-cut Group 1 patient without comorbidities. On the right, you see the isolated Group 2 pulmonary hypertension and high wedge, normal PVR. And then there's everything in between and a lot of considerations that need to go into correctly diagnosing those patients and deciding whether or not they are good candidates for PAH-specific therapy.

So as we think about our treatment choice, we have to consider many, many things. Risk scoring is something we don't have time to talk about, but these comorbidities can impact risk scores. They can impact the symptoms and the severity of the pulmonary vascular disease. We need to think about not just the hemodynamics, but also the RV. We need to think about patient factors. So a lot of this goes into a treatment decision.

So just to remember, PH itself is common, right? It's very common. PAH is rare and, more often than not, even the new patients that I see in clinic are more likely to have Group 2 and Group 3 pulmonary hypertension. However, even patients that we think have Group 1 PAH are increasingly being diagnosed at older ages with common comorbidities. And the most critical thing in terms of making a treatment decision is getting the diagnosis right. And Brad so eloquently went through those issues, and I won't reiterate them.

Most recent clinical trial data have included patients with PAH and multiple comorbidities, although there were often hemodynamic criteria greater than the current hemodynamic criteria for diagnosis, so often a PVR greater than 5. And there was benefit in these patients despite them having their comorbidities. But it is important to remember that we need to monitor side effects and how they tolerate the therapies. And as we decide about treatment escalation, we need to consider how comorbidities impact risk assessment. Functional class, hall walk are both impacted by comorbidities and those are major factors in risk assessment.

So I thank you for your attention.

Chapter 4: Question & Answer Session

Dr. McLaughlin:
Tom, the first question I'm going to direct towards you. You did a very nice overview of some of the newer therapies that are demonstrated to be efficacious in left heart disease. This question is are there any data to support the use of SGLT2 inhibitors in PH itself?

Dr. Cascino:
So it's a great question. We highlighted the data that has been published looking at SGLT2 inhibitors and what they do to mean PA pressure in patients with heart failure. There is no current published data that I know of related to SGLT2 inhibitors in pulmonary arterial hypertension, or Group 1 pulmonary hypertension.

Dr. McLaughlin:
Okay. And I think really what you highlighted is something that we struggle with in clinic all the time, right? Like, we have patients referred that really have Group 2. And maybe, Brad, you can kind of try to explain how you give advice to referring physicians when they send the 75-year-old woman with hypertension, diabetes, enlarged left atrium, a normal RV function and RVSP of 50 on echo who's short of breath. And inevitably, these patients come to us thinking that we're going to cure them, right, thinking that we have this magic pill for them. How do you explain that to both the patient and the referring physician?

Dr. Maron:
That's a great question, Val. Thanks very much. I first empathize with the referring clinicians because it's really challenging to have a patient that's symptomatic in your office with an elevated pulmonary pressure and not want to try to treat them to the best of your ability. The fact of the matter is that even though we all want to do that, the data just simply do not support a first-line approach to using pulmonary arterial hypertension treatments, the PAH drugs, for that indication. And in fact, many of the clinical studies that have been designed to look at this question suggest that there's a signal to harm in some subgroups. Exactly determining who that is remains an ongoing question. But on the balance, there just isn't enough information to warrant the indiscriminate use of those drugs.

In patients who are end stage or are severely symptomatic, there is always room for individualized care decision-making and palliation is

always something to consider for that approach. But by and large, I try to empathize first, acknowledge that treating underlying causes of left heart disease, now with a wider armamentarium of therapies, including making sure you have the right drugs aligned with the right left heart disease problem, as was mentioned earlier for those with, say, hypertrophic cardiomyopathy or amyloid cardiomyopathy. There are now disease-specific treatments that can be very effective at mitigating symptoms in those patients. So it's a shared decision-making at the end of the day, but there's really no data to justify a clinical benefit for the use of those PAH drugs. So we have to work the underlying problem more aggressively.

Dr. McLaughlin:
Great. Yeah. So it's a real challenge.

Tom, you are doing a lot of work on implementation of guideline-directed medical therapy and we see some of these patients who are not optimized. First and foremost, diuretics. How many times have you seen the little old lady that doesn't want to take their diuretic cause they have to pee so much, and it's actually a lot of burden on the provider's office to very aggressively manage diuretics.

But the data suggests that we aren't doing as good a job as we should be with optimization of well-proven guideline-directed medical therapy. So what advice do you have to try to escalate the standard of care and really get these patients the underlying left heart therapy that they need?

Dr. Cascino:
Yeah. So I think, and it adds to what Brad was highlighting, in the end, with all these therapies, is that we're doing shared decision-making with any therapy that we do. And so much of the visit is spent talking about the underlying cause of symptoms as well as the therapies. And I think talking with patients not just about the therapies but the why of therapies. Talk about how diuretics will help with symptoms, and then talk about how, for heart failure with reduced ejection fraction, for example, we know only 25% of people who are eligible for drugs are on all 4 drugs. Talk about the 4 individual drugs. Talk about why we're starting these drugs. They help people feel better, do more, and live longer. And then come up with a plan to get the medication started. And I think central to that 4 medications sounds like a lot, is having close follow-up and getting set up with close follow-ups to make sure that you're monitoring any labs that need to be monitored, but also for symptoms and to answer questions.

I think, more than anything, as people are starting new therapies, being around to be able to answer questions, alleviate concerns, and recognize that all medications have some downside and work through the symptoms that are developing, recognizing that the benefits of these drugs is so great.

Dr. McLaughlin:
Yeah. It's a process, right? And it doesn't happen overnight. It takes a lot of education.

Brad, we've done so many trials that Tom has highlighted that you've also mentioned that have not demonstrated efficacy of PAH therapies in patients with combined pre and post or left heart disease. Why do you think that is? Do you think these drugs are really dangerous? Do you think there's been flaws in the clinical trial design? Do you think we're not enrolling exactly the right phenotype in those trials?

Dr. Maron:
Yeah. It's a great question. In some ways the million-dollar question right now because, if we were able to identify an effective drug for this huge universe of patients, I think we would see a grateful community among patients because they are burdened by their syndrome.

My own view is that the therapies that are so effective in pulmonary arterial hypertension do so through the pulmonary arterial vasculature. But if you think back to the anatomy of the heart and lungs, the most affected structure from the left atrial hypertension, from pulmonary venous hypertension, are the pulmonary veins. And we really don't have good therapies that are known to target that vasculature, and it's easy to assume that they're the same compared to the pulmonary arterial vasculature, but we really don't have reason to think that. So part of the answer is that we just don't have perhaps the right drugs yet. The other answer to the question, though, is that in the clinical trials that have been done, there are subgroups that seem to be responders. The problem and the challenge right now is identifying them up front, and we really don't have clear insight into how to do that and so we take a risk by giving those medications out without understanding who is best going to potentially respond, since the patients that we're giving them to in our own clinic offices could also be those for whom harm has been implicated or simply adding another drug to an existing polypharmacy problem among this aging population, which doesn't need that. And so those are some of the two biggest challenges I think we face.

Dr. McLaughlin:
Tom, you want to add anything to that?

Dr. Cascino:
Yeah, I think everything Dr. Maron said, and then I think additionally, I think about the clinical trial design. Making sure that we know hemodynamics before, when we're enrolling patients in clinical trials. Many of the trials identified heart failure populations and didn't necessarily target a combined pre- and postcapillary PH. Now the more recent trials are, and we're still not seeing positive results, but I think really phenotyping the patients with all the information that we have, including right heart cath, which we know is so critical to the diagnosis, is a path forward.

Dr. McLaughlin:
Great. Well, we are almost at the top of the hour and I'm just going to allow each of you to take maybe one minute to highlight the one or two most important points that you want the audience to take home from our session today.

So, Brad, I'll start with you.

Dr. Maron:
Well, thank you very much. I would say the most important point for the diagnosis is just remembering to consider all the information you have at your hands.

Pulmonary hypertension is much, much more common than pulmonary arterial hypertension, as Val so clearly stated. And you know the answer to the question; you just have to use the information. That's part of how you diagnose patients.

Dr. McLaughlin:
Great. Thank you. Tom?

Dr. Cascino:
So step 1 and step 2 in terms of the treatment algorithm is really making sure that we have the right diagnosis and then targeting that diagnosis. With many of the causes of left heart disease, we have new therapies that are being developed. Make sure we know why pulmonary hypertension has been developed. And then really using therapies that treat the diseases that are causing the pulmonary hypertension in the first place is really where we need to focus.

Dr. McLaughlin:
Yeah. And so I think that's great, and I will add, starting in the same place that both of you started in terms of treating patients with PAH, we need to make sure the diagnosis is correct. And it can be very complex, especially as we see older patients with comorbidities. So really assess the patient as a whole, their clinical risk factors for group 2,their echo, their RV, their hemodynamics, and really have a sense of whether this is really significant PAH and they just happen to have a comorbidity, or if they have pulmonary vascular disease with some comorbidities that you might treat a little bit more gingerly, or if they really have Group 2 and have been so well-diuresed that their hemodynamics meet the PAH definition. And you have to challenge those patients with volume or exercise in the cath lab and really get to the correct diagnosis. So we all start with the correct diagnosis, but I would say it's important not to hesitate to treat someone who has real deal PAH just because they have a well-controlled comorbidity or two.

So, you guys, this was such a great session. It's such a common problem. I really hope that our viewers took a lot away from this. It's something that we deal with every single day. And, Brad, Tom, thank you for wonderful, clear presentations, and I'd like to thank the audience for joining, as well. Have a good rest of your day.

Dr. Maron:
Thank you.

Dr. Cascino:
Thank you.

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