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Pulmonary Hypertension: Getting the Right Diagnosis and Knowing When to Refer

Announcer:
Welcome to CME on ReachMD. This activity, titled *Pulmonary* Hypertension: Getting the Right Diagnosis and Knowing When to Refer" is provided by TotalCME, LLC and is supported by Actelion Pharmaceuticals US, Inc., a Janssen Pharmaceutical Company of Johnson & Johnson.

This replay of a live broadcast discusses the importance of making the correct diagnosis and the timing regarding referral for patients with pulmonary hypertension.

Dr. McLaughlin:

Making the correct diagnosis and knowing when to refer patients with pulmonary hypertension is important. Join us as we discuss 2 very different patients with pulmonary hypertension and the very different care pathways for Group 1 and Group 2 PH patients.

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

Dr. Saggar:
And I'm Dr. Rajan Saggar.

Ms. Burks:
And I'm Marsha Burks.

Dr. McLaughlin:
Great. Well, we have a lot to discuss today, and we're going to use some real cases to try to make this very educational for everyone. And I'm just going to present this first patient, and we'll discuss the implications for referral and treatment.

So this is a patient who's 75 years old. She has a number of comorbidities, including diabetes, hypertension, obesity, her BMI is 34, and atrial fibrillation, and she has a 2-year history of dyspnea that she presented to her primary care provider with. She's on dual antihypertensive therapy and a DOAC for atrial fibrillation. And on physical examination, her blood pressure was not really well controlled and she had a little bit of edema as well. He ordered an echocardiogram, which showed an RVSP of 45, but some other important findings as well, including left atrial enlargement, left ventricular hypertrophy, and normal RV size and function. And we have heightened awareness of pulmonary hypertension so much over the recent years and decade that people see an elevated RVSP and they say, "Oh, should I refer this patient to a pulmonary hypertension center of excellence?" And I certainly get patients like this referred to me all the time.

So, Dr. Saggar, tell me your impressions about this patient.

Dr. Saggar:
Yeah, thanks. Thanks, Val. So I think, as you suggested, this is a very typical type of patient that we see with an echocardiogram suggesting mild pulmonary hypertension. But more importantly, there's pulmonary hypertension, and everyone wants to know, well, is this a patient that we should refer? Is this a patient that needs pulmonary hypertension-specific therapy?

I think, out of the gate, one of the things we focus on, of course, is the patient's history, their age, and sort of putting together the story. So we know that the echo suggests pulmonary hypertension, but we kind of come back and look at the data. And one of the things that we sort of look for right away is, and we remember right away, is that if you take an echocardiogram that shows pulmonary hypertension, and you take 100 of them for instance, the majority of them that have pulmonary hypertension are going to fall into some form of pulmonary hypertension that's not Group 1. Group 1 being the PAH category where we have all these medications available. But actually, most of them fall into Group 2 pulmonary hypertension, which is pulmonary hypertension related to some form of heart disease or valvular disease, basically some issue with the left heart, or some type of Group 3 pulmonary hypertension, which is pulmonary hypertension related to some form of lung disease, or a lot of times a combination of the 2.

So in this particular patient, out of the gate, we noticed that the patient's older. And we have realized that pulmonary hypertension, even Group 1 PAH, we're seeing in older patients, generally speaking, today, compared to, let's say, a couple decades ago. But this patient is a septuagenarian, well into her 70s. So that's clue number one that we may be dealing with not a Group 1 patient. But we don't want to just use the age right? We see the diabetes. We see these, what we call, comorbidities in this world. And everyone's aware of metabolic syndrome, but diabetes, systemic hypertension, obesity. And then one other one that catches our attention is either paroxysmal or chronic atrial fibrillation, which is sort of a light, a bulb goes off there, because that often suggests that the left atrium may be enlarged, and that sort of builds the story, the comorbidities and the atrial fibrillation, for a patient who may have some form of left heart disease driving the pulmonary hypertension. There's a 2-year history of dyspnea and if you delve in a little bit more in that you might find that it's been sort of persistent, not progressive necessarily, which we often see in our Group 1 patients.

The patient is already taking 2 antihypertensive therapies, and as you mentioned, a blood thinner for atrial fibrillation. And then on exam out of the gate, the vital signs, the patient has uncontrolled systemic hypertension, right, despite the 2 antihypertensives. So clearly, we haven't optimized that, which is the sort of rule 101, if you will, for dealing with patients who have pulmonary hypertension with the Group 2 setting. And there's already lower extremity edema and this patient's not on diuresis. So as you know better than I do, the world of preserved ejection fraction heart failure, assuming that's where we're taking this, the therapies up till recently have always just been get some fluid off and control the blood pressure.

So out of the gate, we can sort of look at this echo here that you can see in front of you, and sort of what jumps out at you is the left side of the heart, which looks sort of like the mirror image of what we'd see with someone who has Group 1 PAH. We see a really large and hypertrophied left ventricle and we see a large left atrium. And the right side of the heart looks squished, if you will, which is what we see oppositely, right, in the Group 1 pulmonary arterial hypertension patient. And the apex of the heart on this 4-chambered view is sort of all left ventricle, if you will. And usually in patients who have Group 1 PAH, it's sort of more of the right ventricle that shines at the apex in that setting.

So we're sort of building a story here for someone who, out of the gate, the pretest probability is more concerning for a Group 2 pulmonary hypertension phenotype.

Dr. McLaughlin:
Yeah. I think that was a great summary, Rajan. I just want to make a couple of points about the echo as well, because one of the most common questions I get asked by frontline primary care providers is, “Okay, at what RVSP should I refer?” And that's not a question I can answer. An RVSP of 45 could be very different in different scenarios. So in this case, the RVSP is 45, but the right side of the heart looks absolutely normal, and the left atrium is big, the left ventricle is thick, that probably they have Doppler indices of diastolic heart failure or diastolic dysfunction. And so that's a different scenario than if the RVSP was 45 and the left heart was normal and the right heart was big and dysfunctional. So I think you really nicely pointed out the other findings on echo that are so important beyond that RVSP.

And you also pointed out some of the other things we look at for Group 2 disease, some of the historical factors, the risk factors for metabolic syndrome, some of the symptoms, like orthopnea is more common in patients with elevated left heart filling pressures. And so we may have the same or different approaches to this because I get these patients all the time in clinic too. So at what point do you say, I'm going to use a calculator or my clinical impression for the pretest probability and say this is highly likely to be Group 2 disease and optimize all the other line, you know, the blood pressure, the volume, the obesity, the diabetes, as you say, versus when do you move on to a cath? Maybe you can go through your thought process on that, Rajan.

Dr. Saggar:
Yeah, I mean, and just to kind of add to what you just said and answer your question, I think if you had, as you know, we are seeing a lot of patients, even with Group 1 PAH, diagnosed later in life, in their 60s. So this patient could have comorbidities but still have Group 1 PAH. But as you pointed out, the echocardiogram – so the comorbidities themselves give you a pretest probability, but the echocardiogram really helps here because you really get to see that the findings here are more consistent with the echo of someone

who has a left heart disease primary problem as opposed to a right heart disease primary problem.

But to move this a little bit further, I think there's some nice scoring systems that have sort of been elaborated over the last several years. And the one I tend to use, just because it's a little bit easier, is this H_2FPEF scoring system where they basically are trying to determine the pretest probability of, again, preserved ejection fraction heart failure. We're assuming the ejection fraction in this patient up on the left ventricle is normal, which, I'll just throw that out there, it is. So we're talking about preserved ejection fraction heart failure. And this H_2FPEF scoring system is 1 of 2 that are out there. You can see the other one on the screen here is the HFA-PEFF score. But the H_2FPEF score includes factors like age, the body mass index, and echocardiographic finding, the so-called E/e' ratio. It includes the pulmonary artery systolic pressure, which, by definition, if it's elevated is adding to the pretest probability that the patient has preserved ejection fraction heart failure, to the point we just made. And then it has atrial fibrillation as well in there, the presence or absence of atrial fibrillation. And then it gives you a pretest probability, the likelihood that this patient in front of you could have preserved ejection fraction heart failure.

The HFA-PEFF score is another very valid and usable tool. It requires a little more information. It sort of has 3 different domains with a functional domain, a morphologic domain, both for echo, as well as a biomarker domain for brain natriuretic peptide, and age, gender, etc.

But the point is that a scoring system here is actually pretty helpful, especially if you're sort of wondering whether this person is straddling, if you will, between a Group 1 phenotype or a Group 2 phenotype. And as we mentioned earlier, sometimes the water gets a little muddy there sometimes, in which case a referral is valid. But I think this case, we're really making a case for the idea that, look, this is going to be somebody who probably has a high pretest probability for preserved ejection fraction heart failure, which is a Group 2 PH phenotype, uncontrolled systemic hypertension, and extra edema on board; modifiable things that you can actually do, actually treat in your own clinic to optimize, before you sort of re-evaluate that patient and her symptoms, and then you can sort of redetermine whether referral would be appropriate.

Dr. McLaughlin:
I think that was a wonderful summary. And this is one of the things I call bread-and-butter medicine, which too often gets overlooked, right, to make sure the blood pressure is at target, to make sure the patient is volume optimized. And let's face it, adjusting diuretics and potassium and all of that, it's a lot of work; it's something that sometimes is not paid as much attention to as we would like. And so I think that's a key issue of making sure we're managing all the underlying problems as best as possible in such a patient.

And then there's emerging data on the use of other therapies such as SGLT2 inhibitors and GLP-1 agonists in patients with chronic heart failure with preserved ejection fraction. And so this is, I think, a team sport, really. I don't think, at least at our center, we don't have capacity to do all of this for all of the HFpEF patients that get referred to us. And so this is, at least in our practice, where a good partnership with the local primary care provider and local general cardiologist is really critical.

Dr. Saggar:
Absolutely. Absolutely.

Dr. McLaughlin:
So these patients are very common, and we just kind of wanted to go through, you know, common things happen commonly. But let's move on to another patient, a patient that is going to fall more into the Group 1 prototype, which we really want to be recognized early in the community and referred early because we have very effective therapies for these patients.

So this is a 27-year-old woman without any prior past medical history, and she presents to her primary care provider with a 3-month history of dyspnea, which is progressing despite her trying to take really good care of herself, really watching her salt, trying to exercise. Her dyspnea is getting worse and she's Functional Class III by the time she gets to the primary care provider.

He does an echocardiogram, and again, the RVSP is 45, so very similar, but the right ventricle is enlarged and dysfunctional. The left atrium is normal in size. The left ventricular ejection fraction is 60%, and the left ventricle morphologically is normal. The NT-proBNP is 1,000 and the 6-minute hall walk is 350 meters. And as I said, she has Functional Class III symptoms. Her GFR is normal. Her blood pressure is normal, systolic of 120, and her heart rate is 89.

So, Rajan, I gave you the exact same RVSP on the echo of 45, but this is a very different patient, very different history, very different other echo findings. So tell me your initial thoughts about this patient.

Dr. Saggar:
Yeah. So you pointed out earlier that if someone asked you, “What's the RVSP that you should refer at?” – and again, these 2 cases really highlight why that's a difficult question to answer, right? The RVSP here is 45; it was 45 in the other case. But this is a very

different history and a very different prototype of a patient, right? So obviously, we're talking about the extremes of Group 1 PAH and Group 2 PAH, but, and like we said earlier, it does get muddy in terms of these phenotypes sort of getting blurred.

But this case is very different from the 75-year-old we just talked about, and we expect to see, well, we have this progressive symptomatology over a 3-month period, a relatively shorter amount of time, a relatively younger individual, a female. Obviously, females are more likely to have Group 1 PAH. But then is, really, the money is going to be in the echo, right? We have a good blood pressure, a good heart rate. We obviously have an NT-proBNP which is elevated at 1,000, like you said, a compromised 6-minute walk distance, and functional symptoms, which is really concerning, right, in someone who's 27 years old with the Functional Class III symptoms, and normal renal function. So the echo here, we would expect a very different set of findings, right? We would expect, perhaps, instead of the left heart looking large and thickened, particularly the left ventricle and the left atrium, and we would expect – and squishing, if you will, of the right side, which is what we saw in the first case. We sort of see the opposite in patients with the Group 1 PAH phenotype where we really have an enlarged right-sided chambers with right atrial enlargement, right ventricular enlargement. Sometimes we see right ventricular hypertrophy, and then we sort of see the septum sort of bowing into the left side or straightened and a squished left side of the heart. Sometimes we see a pericardial effusion, which is noted to be a negative prognostic factor in Group 1 PAH, when you do see it.

And that's kind of what we'd expect to see in this patient. And we'd see a really preserved ejection fraction on the left side, and the left side would be spared of valvular heart disease, etc., so there wouldn't be a concern for left-sided dysfunction or issues on the left side, so to say.

Dr. McLaughlin:
Yeah. And that was a great summary. And I think the points that you made are so critical, like just looking at that echo, in addition to the patient's age and lack of other medical history, the concern for Group 1 of pulmonary arterial hypertension is high. And that's the sort of patient we want the primary care provider or the frontline cardiologist or pulmonologist to refer as quickly as possible to a PH center for the rest of the workup, which is obviously going to include a lot of other testing, including a right heart catheterization.

So now we've moved this patient to the PH center. And one of the most fantastic things about dedicated PH excellence centers is that we have a whole team, including our wonderful nursing staff, who is highly trained in this specific disease.

So Marsha is one of our nurses here. I have the privilege of working with her every single day. I'll tell you, if I ever get sick, that's the voice on the other end of the phone I want. But, Marsha, you've talked to hundreds or probably even thousands of patients with PAH. Tell me a little bit about what you chat with them about after the doc leaves the room, right? They're always going to have more questions after we leave the room. And you guys are so important with educating these patients about the disease and about the therapy. So tell me a little bit about how that goes for you.

Ms. Burks:
Absolutely. Thank you so much, Dr. McLaughlin. I like to begin educating a newly diagnosed patient by asking them their understanding of their diagnosis and what they know about pulmonary hypertension. They have just been given a lot of information and a serious diagnosis, and that all can be quite overwhelming for patients, so just understanding where they're at is always the best place to start for me.

I like to explain pulmonary hypertension to them as just as you have a blood pressure in your arm, you have a pressure in the vessels of your lungs. And when that pressure is high, it causes strain on the right side of your heart and leads to enlargement and dysfunction of your right ventricle and that is what's causing your shortness of breath.

Being diagnosed with a chronic illness like pulmonary hypertension is life-changing for these patients, and as Dr. McLaughlin said, we love to have a close relationship with them and let them know that we are their team. We do want the patients to take an active role in their care and use shared decision-making when we discuss their medical management going forward. We have written materials that we provide to our patients. The Pulmonary Hypertension Survival Guide is a great tool, referring them to reputable websites that contain accurate information. Many programs have PH support groups that we can get them connected with. Also peer mentors, sometimes talking to another patient that has been through what they are going through can be very impactful. Speaking to someone that is successfully living with pulmonary hypertension can be very encouraging to a newly diagnosed patient.

Of course, we have many medications that we are going to review, and they all come with their own set of side effects and management strategies, but we want them to know that we're there to help them with each step of that process.

Many lifestyle changes need to be discussed during the education process, changing their diet, heart-healthy diet, limiting their salt. They could benefit from a referral to a nutritionist to really help them figure out their diet and fine-tune that. Staying active is also so

important. Even though they might be fatigued and short of breath, maintaining an active lifestyle is very beneficial. Referring them to a structured exercise program like pulmonary rehab can give them the start they need with that. It can give them more confidence in exercising and help them understand their limitations.

Their quality of life can be significantly impacted. Normal daily activities can be hard for them. They may experience social isolation due to their physical limitations. They may have feelings of guilt or feel like they're going to be a burden to their caregiver. PH treatment and care can be expensive, so they might be thinking of financial strains or putting a financial strain on their family. Job considerations, some patients may have a very physical job that they can no longer keep up with, or just the daily stressors of a job can be a lot for a pulmonary hypertension patient. Taking time off for testing can lead to a lot of missed work and could put strain on their employment. They may benefit from speaking to a social worker. They have various community resources that they can share with the patients. And many patients have anxiety and depressions, and I think that we need to acknowledge that and provide them resources to support groups or help them get connected to a mental healthcare professional in their area.

Pregnancy prevention is also such an important topic. Pregnancy in PH is potentially life-threatening, so it's important to have these conversations early with patients of childbearing potential. And many of our medications can also be harmful to take during pregnancy, so these medications have monthly pregnancy test requirements that we should start discussing that as part of their education as well.

Dr. McLaughlin:
Great. Marsha, that was a wonderful summary. Thank you so much.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Vallerie McLaughlin, and here with me today are Dr. Rajan Saggar and Marsha Burks. We're discussing making the correct diagnosis and knowing when to refer patients with pulmonary hypertension.

So, Rajan, let's go back to the patient. And we've met them. They've met with our nurse. We are doing the rest of the testing and the right heart cath, confirming the diagnosis, and all of those details. Let's talk about the important steps on which we base our treatment. And we know that risk stratification is so critical; it's really ingrained in the treatment algorithm. Tell me a little bit about the different tools to calculate risk and how you apply this in your practice.

Dr. Saggar:
Yeah, so, as you said, once you've made the diagnosis of Group 1 PAH, then we have several calculators available to assess sort of risk at diagnosis. And the risk we're talking about, essentially, is similar across the spectrum of different risk calculators. It's really assessing the risk of death, essentially, over the first 1 year of their PAH diagnosis, from diagnosis to the first 1 year. And this is really important because as we've all sort of alluded to here, the mortality of this condition is high, and so we want to start therapies and optimize those therapies out of the gate.

So the risk score really sort of allows the provider an objective way to determine initial therapeutic strategies, and so you're optimizing that out of the gate. So an example of that – and again, as I mentioned, there's several calculators, and I think the message here is that we want to use a calculator. Whether you choose the REVEAL calculator or another one of the calculators available, using some form of risk assessment makes a lot of sense. And we'll talk about it not only at diagnosis, but also at follow-up when you see the patients back in the clinic.

So here's an example in front of you of the REVEAL risk calculator. And there's a couple of them. There's the REVEAL Lite 2 risk calculator, and there's the regular sort of larger, more parameters to look at for the REVEAL 2.0 calculator. So this is one of them, and you can see here that they have, if you jump online, for instance, you can find these calculators very easily, very quickly with any search engine. If you just put in PAH risk calculator, you'll get multiple calculators that you can choose from and you'll find one that fits your practice. But they'll have parameters, such as this one. And these are highly vetted and validated modalities. So they're not just made up, right? A lot of statistical work has gone into making these calculators. So they're very vetted and they're also updated with time and they get more and more refined over time. So I think using one of these calculators makes a lot of sense.

So you put your data in there and the data doesn't have to be there from the very day that you are evaluating the patient; it can be in the recent months even. You're sort of trying to put all that data into a calculator and then predict a risk score. So out of the gate, we have low risk, intermediate risk, and high risk. So we call it the 3-strata system, out of the gate, in terms of diagnosis.

And here's another example, the ESC, the European Society of Cardiology and European Respiratory Society have stratification models as well with this 3-strata model. And you can see up there, if you're looking at the score on the left, you can see the horizontal column, that it says determinant of prognosis, which is an estimated 1-year mortality, and you can see the risk for that. So low risk is less than 5%, intermediate risk is 5% to 20%, and then, most importantly, the high-risk patient, so these are patients who you calculate the risk for at diagnosis, they have a greater than 20% risk of death at 1 year.

And again, you may not have all of the parameters available at one point, and each calculator has a minimum amount of sort of variables that you want to make sure you put in to actually use the calculator. So that's what we do at diagnosis.

And then, just to follow that up, in the follow-up of patients, we use a 4-strata model because we realized that the intermediate risk group was very large and could be discernible in terms of the survival, in terms of prognosis, right? So the folks making all these calculators have done a great job dividing that group into sort of an intermediate-low risk and intermediate-high risk. So you end up with 4-strata models in the follow-up.

And this is something we do routinely when we follow up the patient, because at the end of the day, what's the goal? The goal is to get all our patients down to that green low-risk column. And when you're not there, you need to figure out how to get there.

Dr. McLaughlin:
Rajan, that was just a wonderful summary of the objective risk calculators that we have, which are really, really important to do. They're really important to do. And we do that in clinic every time we see a patient.

But I do want to acknowledge that there are other factors that could affect our treatment choice. Like the objective score has to be the anchor of it, but sometimes I think of the objective risk score as not entirely reflective of that patient. And I always give 2 examples on different extremes, right? These are totally extremes; I get it. So my 70-year-old, 5'1" woman with scleroderma is never going to be Functional Class I and is never going to walk 440 meters. And no matter what I do, she's not going to be low risk by an objective score, even though she might have improved or even normal hemodynamics, normal RV function on therapy, but she's never going to be low risk.

And on the other hand, I might have a 6'1" gentleman who's 20 years old with heritable PAH. And he can walk 450 meters, but his predicted is 700 and he's always going to be Functional Class I or II, but he could have really bad RV function and I could be really worried about him. So there are, I think, opportunities for other factors, particularly the RV on imaging, to complement the objective risk scores.

And then I think the other things that we need to take into account as we think about treatments are the comorbidities. Do they have something that might get worse if we treat them very aggressively? Are things like their age, their quality of life, goals, their social support – there are some patients who don't have the ability or the support system to do complicated pump therapies – the side effects and the like. Hemodynamics, kind of like with RV function, can complement the objective risk scores.

But I do think it's important to acknowledge while risk scores, like objective risk scores, are critical, we should do them every time we interact with the patient, there are other things that go into the treatment choice.

Do you want to add anything to that, Rajan?

Dr. Saggar:
No, I think that was a great summary. I think the point there is that if this was low risk, do this; intermediate risk, do this; high risk, do that, and it was that simple – we wish it was that simple. But like you said, there's so many different factors that come into play. And so that's where the shared decision-making comes in with the patient and with their family sometimes to make the best choices. And sometimes we don't make the best choices up front. We try to be perhaps more aggressive in the patient's interest, of course, and sometimes we have to back off. And a pump that we thought would be ideal for a patient, and perhaps could have been ideal, just doesn't work for that patient for so many different reasons. And there's so many different examples of the nuances of why one drug or the treatment choices you make may be different than perhaps the algorithm might suggest would be the ideal way of doing things.

Dr. McLaughlin:
Yeah, that's a great point. I mean, everyone focuses on that initial treatment decision, but I think the even more important thing is the continued reassessment and how they're doing on that therapy, how they're managing the therapy, what their side effects are like, and adjusting. And it's really not just a science; there's an art that goes into that too. And it's complicated. It's really more complex than when I first started doing pulmonary hypertension. The year I started doing pulmonary hypertension was 1995. One therapy was approved, and now we have more than a dozen therapies. So the conversation back then was very easy. You have pulmonary arterial hypertension; this is the option. And now it takes a lot more time and to go through all of that with the patient, and it's much more complicated.

So we have a number of oral therapies, including the endothelin receptor antagonists. Three are FDA-approved in the US: bosentan, ambrisentan, and macitentan. We have 3 therapies that affect the nitric oxide cyclic GMP pathway, so sildenafil and tadalafil are PDE5 inhibitors approved for PAH. And riociguat is an sGC stimulator approved for PAH and CTEPH, the only therapy that's approved for CTEPH. We have a number of prostacyclin analogs: IV epoprostenol, the first one approved that I mentioned; we have treprostinil,

which can be delivered in a number of ways, including IV, sub-Q, orally, and inhaled; and iloprost can be inhaled as well. We have the prostacyclin receptor agonist, selexipag. And then the newest therapy available is the activin signaling inhibitor, sotatercept. And I should add also that the combination tablet of tadalafil/macitentan was approved in March of 2024. So a lot of different choices.

And as we talk to our patients, a lot of things go into this decision. Most patients go on a PDE5 inhibitor/ERA combination at the time of diagnosis. Those patients who are very high risk, they may go on to a parenteral therapy, but the majority of patients go on to ERA/PDE5.

So, Marsha, tell me a little bit about your conversation with those patients as those therapies are prescribed and how you think that combination tablet fits into clinical practice.

Ms. Burks:
Well, we typically use a staggered approach when starting PDE5 and ERA combination, meaning we start one medication for a week, see how the patient's tolerating, things are going well, we'll add in the second medication, give it another week. And if they're tolerating both well, then we can start the conversation about potentially switching them to the combo pill. And of course, we go over the side effects of each of the medications. And if they are having a side effect from one of them, by starting it with a staggered approach, you can kind of tell which medication is the culprit and which you might need to adjust.

Dr. McLaughlin:
Rajan, do you do the same thing? Or do you start the combination tablet in newly diagnosed patients?

Dr. Saggar:
Well, it's funny. I was about to ask Marsha, so you do the staggered approach because it's good medicine, like starting 2 medicines at the same time, you know, side effects, etc., it's tough to tease out what's what. So staggered approach is always what we do and we fully agree. But on the ground, realistically, now that the combination is available and they do have sort of the lower dose and you can titrate up to the higher dose, given your experience with so many patients that you've staggered over the years, do you feel like there's enough patients that have an issue with starting one after another? In other words, would you surmise that there would be a problem if you went straight to the combination? Because I think that's what a lot of people would like to do. I think it also complicates the starting 2 drugs, stagger it, and then switching to a pill. It's a lot of insurance, it's a lot of work on the ends of our staff and our pharmacy staff and just our people that have to put these authorizations in. As you know, this is no walk in the park. So I just wanted to know if you guys have dabbled in with starting it up front. I haven't yet, but I'm thinking about sort of moving in that direction.

Ms. Burks:
I have one that I'm getting ready to but not quite approved yet, but it will be a totally treatment-naïve patient that we will starting on the combo pill. So I'm anxious to see how it goes.

Dr. Saggar:
More to come. Yeah, this drug, as you know, this combination pill was just approved, so I think we're also getting our feet wet here. But I think we'll probably see more of the initiating the combo out of the gate.

Dr. McLaughlin:
Yeah. And I think there are some people who do it. I always feel like if they have a headache, do you know which one it was? Or certainly lower extremity edema is something that you think is more likely the ERA. But that's just how we've done it. But I know there are people who start the combo pill out of the bat. And of course for established patients who come back on the individual tablets, we always offer the combination pill. It certainly can ease their pill burden and their copays. But so that's usually the first step. High risk, you know, parenteral prostacyclin plus oral therapy, and not high risk, ERA/PDE5.

And that's, again, we talk about that initial decision, but I think even the more complicated and important decision is what you do with that next follow-up and even the next follow-up. As Rajan said earlier, the goal is getting the patient to the low-risk status. And now with the 4-risk strata calculator, I think it's a lot easier to have those discussions, because that intermediate-risk group is a big group, right? There's some that I'm a lot more worried about than others. And so now dividing that, using the calculator into intermediate-low and intermediate-high risk, I think, makes that conversation a little bit easier for the patients.

So, Marsha, let's just go back to the oral therapy very briefly. We talked a little bit about the combination tablet and the copay and pill burden and that sort of thing. But I think another important point for nursing is really following these medications because they often, both the ERAs and the sGC stimulators, have the potential for teratogenicity. And this is a touchy subject, right? The patient gets this diagnosis which is not a good diagnosis. I mean, they're overwhelmed with that. And then the whole conversation about you really shouldn't have children, and then the conversation about what birth control are you going to use and monitoring the risk of pregnancy or

testing for pregnancy along the way with some of these therapies. So it's a tough conversation. Tell us about how you manage that.

Ms. Burks:
It is very tough and it might be a conversation you need to have multiple times with the patient. But pregnancy, I do think we need to be very conservative and let them know that having a baby with pulmonary hypertension is potentially life-threatening, so it is something that needs to be discussed early, discussed often. And you know some of these medications have effects for the baby as well. So if you get pregnant and don't know you're pregnant and you're still taking your medication, you might be doing harm to your fetus and not even realize it. So that's why the monthly pregnancy tests are important with certain medications. And pharmacies shouldn't be dispensing unless you have your monthly pregnancy tests completed and we know that it's negative. But yeah, it can be very difficult.

And then just discussing the different forms of birth control, there are some better than others. You know the IUD, progestin-only IUD, is typically preferred. We like to avoid estrogen oral contraceptives or patches due to the venous thromboembolism risk factor there. And tubal ligation would be a more permanent conversation that would need to be had if that's the route they would want to go.

Dr. McLaughlin:
Yeah, it's tough. Thank you for all the time you spend having those conversations for our patients.

So let's move on to our final thoughts for this patient. So I think it's much different than the first patient. This is the patient where we're really worried about Group 1 PAH, and we want the frontline provider, whether that's the PCP or the local cardiologist or pulmonologist, to really have their index of suspicion raised when they see not just an elevated RVSP on the echocardiogram, but also an impact on the right ventricle and right atrium. Those are the patients where we really think a kind of a fast track to the PH center is really important and then the workup continues at the PH center.

Rajan, let me ask you to take it from there. What are some of your important points that you want to make on this second case?

Dr. Saggar:
Yeah, I think you said it well. They're 2 very different cases we presented. I think the extremes of the 2 phenotypes, the Group 1 phenotype and the Group 2 phenotype, we're going to see. I think one of the take-home messages is that we're going to see a lot more of the Group 2 phenotype. So if you're in your practice and you're seeing an echo that's positive for pulmonary hypertension, or concerning pulmonary hypertension, it's got a much higher chance of being Group 2 than Group 1. But you don't want to miss the Group 1 patient, and you want to make sure that you refer that patient sooner than later because of the mortality associated with that condition.

And that's where your clinical suspicion, your pretest probabilities, looking at that echocardiogram. And we understand, I think, that we rely a lot on the echocardiogram and the read, the formal report, right, which may lack some of the things you're looking for. But again, that goes to your pretest probability. If you're worried about a patient who you think could be having that Group 1 phenotype but the echo may not be sharing with you the criteria that you are looking for to make that evaluation, since I think we concentrated a lot on the echo today in terms of distinguishing these 2 phenotypes, that you may have to make a phone call to your cardiology colleague, and we do this all the time, right, for patients when the testing doesn't give you all of the information that you may be looking for but what good medicine is all about. So we don't want to miss those cases. So that would be another pearl.

And then I think, finally, if you do, in fact, make the diagnosis of Group 1 PAH, I think a referral, as we mentioned, is definitely very reasonable. And our goal as doctors who see these types of patients routinely is to manage those patients with you, together, because you're available. Often there's a location issue, etc., there's distance involved.

And then so that goes back to risk assessment, right? So the last thing we would point out is risk assessment. Not all patients are created equal in terms of their risk of death. So we use these risk tools to sort of make those assessments. And as Val said earlier, they're not perfect and we can't always get patients to low risk, which is our eventual goal, but it gives you a guide, and I think it's helpful, and certainly it's helpful for us to have our colleagues in the community co-managing these patients, or we're co-managing with them, with you guys, with the community physicians. And so I think it's a team effort. So at the end of the day, we want to do what's best for the patient and make sure they survive as long as possible is the goal, with good quality of life.

Dr. McLaughlin:
Yeah, that was fantastic. There was one other thing I was thinking while you were talking, like we really geared this, really, mostly based on the echo and the referring physicians. But we certainly do have the opportunity to understand the difference between Group 1 and Group 2 more if these patients get to the cath lab, right? Let's say there's someone with Group 2 risk factors, but their right heart has some abnormalities and we're going to, for lack of a better word, give them the benefit of doubt and do the cath and find out what they have. Sometimes a fluid challenge during that cath can help us delineate from Group 1 and Group 2. So the story doesn't end just at the echo. I just wanted to add that. I know we didn't talk about it yet, Rajan, but as you were talking, I thought that was an important point to

add.

Dr. Saggar:
Absolutely.

Dr. McLaughlin:
Yeah. And, Marsha?

Ms. Burks:
Yes. Well, pulmonary hypertension education can be extensive, it can be ongoing, and it can change over time, depending on your patient. I think it's important to allow the patients to guide their own education by understanding what they know about their diagnosis and meet them where they are at. There are many medications we have to treat pulmonary hypertension. We have a potential to use combination pills, lessen their pill burden. And we really need, especially with this case number 2 in particular, a young woman of childbearing age, really discuss pregnancy prevention early on with her, especially the need for monthly pregnancy tests, depending on what medications she may be going on.

Dr. McLaughlin:
Yeah. So I enjoy working with both of you, Rajan and Marsha. I learn something every time I chat with you. And I think your commentary today was very important. Rajan, you really nicely highlighted how we want to work with primary care providers and local providers and understand the needs that they have, and how to co-manage patients with them.

As you mentioned, Group 2 PH is just becoming more and more common with the explosive comorbidities our patients have, or the frequency of the comorbidities they have, and the increase in diastolic heart failure or heart failure with preserved ejection fraction. So I think it's important to be attuned to that and really try to optimize those patients' care, often locally. But at the same time, having enough of a suspicion for pulmonary arterial hypertension in those patients who present with dyspnea and other findings concerning for Group 1 disease like the echo in our second patient with right ventricular enlargement and dysfunction. And sometimes it's hard, like that's a zebra, it's a needle in the haystack, but you kind of have to keep your awareness high for that because that is such a fatal disease.

As we've learned, our pulmonary hypertension centers of excellence really specialize in this and have resources, including the wonderful nurses like Marsha who know this disease in and out and spend a tremendous amount of time with our patients, educating them on the disease, on the lifestyle changes they need to make, and on the therapies. And the very methodical risk assessment and escalation of therapy of which we now have many, many options, is really part and parcel of managing our patients with pulmonary arterial hypertension.

So I think everyone has made important contributions today and important points. Rajan, Marsha, any other final take-home messages you want to add?

Dr. Saggar:
Oh, I would just say I enjoyed the conversation. I think, like you said, I always learn a lot. I think we're always learning with this condition. We're always learning from each other. And so thank you.

Ms. Burks:
Absolutely. The same. I have had the privilege for working next to Dr. McLaughlin for 18 years and learning from her, and taking care of the pulmonary hypertension patients has been so rewarding for me.

Dr. McLaughlin:
Well, I'm lucky to have you work on our team, Marsha, it's a pleasure.

So that's all the time we have for today. So I want to thank our audience for listening in, and I want to thank Dr. Rajan Saggar and Marsha Burks for joining me and sharing all of your really valuable insights and expertise. It was great speaking with both of you today.

Ms. Burks:
Thank you.

Announcer:
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