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https://reachmd.com/programs/cme/pulmonary-arterial-hypertension-deeper-dive/12001/

Released: 12/02/2020
Valid until: 12/02/2021
Time needed to complete: 60 minutes

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Pulmonary Arterial Hypertension A Deeper Dive

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Dr. McLaughlin:
Thanks to everyone for being here today. I know that schedules are crazy, and we're thrilled that so many people have joined this live program on *Pulmonary Arterial Hypertension: A Deeper Dive*. I am thrilled to be here with my good friend and colleague, Dr. Rich Channick. Rich, do you want to introduce yourself?

Dr. Channick:
Yeah, hi, everybody, it's Rich Channick, and calling in from the West Coast. So it's a pleasure to be working with Val and a pleasure to be speaking with you about pulmonary hypertension today.

Dr. McLaughlin:
Yeah, and I'm Vallerie McLaughlin. I'm from the University of Michigan. And Rich and I want to make this a very casual program. We want to have a lot of interaction, and we want to have a lot of questions for you, so please feel free to send questions in to the chat, and we'll try to get to them, as many of them as possible.

So let me just give you a little bit of an outline of what we're going to talk about. We're going to talk about pulmonary hypertension, diagnosis, functional classification, natural history, and we are going to focus a lot on risk assessment before we go into the medications.

I think everyone knows that really what brings patients to us is the fact that they just can't live a normal life. They have incredible functional impairment, whether that is reduced exercise capacity—because they want to be more active—or whether they can't even just get through simple activities of daily living or take care of their kids or do their job. They have a lot of exercise limitations. But this also translates into many other areas of their life. They can't do social activities. They can't travel. It also impairs their psychologic function. I mean, this is a very devastating diagnosis, so it has implications for patients with depression, anxiety, trouble sleeping, family relationships and the like, so it's a really challenging diagnosis.

Now, I want to remind everyone that you cannot make the diagnosis of pulmonary arterial hypertension without a right heart catheterization. I think we are all experiencing the patients who are referred to us because of an echo demonstrating an elevated RVSP. And there are many reasons for an elevated RVSP on echocardiogram and many causes of pulmonary hypertension, but to really be called group 1 pulmonary arterial hypertension, one has to go through a very exhaustive diagnostic algorithm which culminates in the right heart catheterization, so this is required to confirm the diagnosis, to calculate resistance, to do vasodilator testing which guides therapy. It also excludes the other potential causes of pulmonary hypertension. Occasionally, we find someone with an

undiagnosed shunt, but really, one of the most common causes of pulmonary hypertension that gets referred to our clinics is left heart disease, is elevated left heart filling pressures from systolic dysfunction, diastolic dysfunction, or a valvular lesion that leads to group 2 pulmonary hypertension.

And I think something that's really important about the cath is determining the degree of right ventricular dysfunction, which has very important implications for treatment. We think of this disease as a disease of pressure. Pressure defines this disease. But in terms of the severity of illness and the prognosis and the decision-making regarding treatment, it's really the function of the right ventricle that is most critical. It's what is the RA pressure and what is the cardiac output or index, and so those are really critical parts of the right heart catheterization.

So, on the right side of this slide, you see the essential components of doing a complete right heart catheterization: the saturations to make sure that we are not missing an intracardiac shunt; the right atrial pressure—as I mentioned, important indicator of right ventricular function; the pulmonary artery pressure of course defines the disease; the left heart filling pressure helps us determine whether this is group 1 or group 2—and again, group 2 pulmonary hypertension is very common; the cardiac output and index—again which are important implications for right ventricular function and the management of therapy; and the calculation of pulmonary vascular resistance, which is really just the pressure gradient across the pulmonary vasculature, so mean pulmonary pressure minus the left heart filling pressure, the wedge, or left ventricular and diastolic pressure divided by the cardiac output; and then, of course, vasodilator testing in a certain population, specifically the idiopathic, heritable, and drug- and toxin-induced, because a handful of them may have a very robust reduction in their mean pulmonary artery pressure with an acute agent such as inhaled nitric oxide, and that has really important implications for their therapy. They may respond to calcium channel blockers.

Now, Rich, you've been doing right heart catheterization for decades I would say. Do you have any pearls that you want to share with the audience about performing a good right heart catheterization?

Dr. Channick:
Yeah, I think the point is that it's not as easy as it seems, and certainly, over the decades, I've seen many instances where you can get misleading information, because there are some critical things. I mean, one of the things is getting an accurate wedge pressure, and I'm sure, as you know as well as anybody, Val, that's easier said than done in patients who have very high pulmonary artery pressure, so one needs to really ensure the accuracy of the wave forms. There's a lot of respiratory variation, where do we measure on the respiratory cycle, so a lot of little nuances to obtaining a good right heart cath.

I think that we learned over the years that the cath is only as good as the numbers that you're getting, and I think in addition, when you think of things like a wedge pressure, because you're going to have such big importance, I mean, we have to look at the big picture, and so... I mean, for example, you have a patient with a borderline wedge pressure that we think is even accurate at 14 or 15, sort of falls within the precapillary zone, but if this is an older patient, lots of comorbidities, obese, where we really have high suspicion for left heart disease and they are on diuretics, that's part of the whole picture, so classifying these patients is more than just about the cath. And I think I would just underscore your point about the measures of cardiac output, cardiac index, right atrial pressure and saturation being far more important than the pulmonary artery pressure itself.

Dr. McLaughlin:
Right. And one of our audience members, our dear friend Teri Trowell, made the important point of where we measure the wedge pressure, and it should be measured at end expiration and end diastole, and that's a really important point. I think, as a cardiologist, we often do LVEDPs with our first right heart catheterization, and those tend to be less difficult in terms of some of the challenges of obtaining them. There is just less room for error with how far the balloon is built up or blown up or where the catheter is. It just makes it a little bit easier.

I think, Rich, you were alluding to some of the challenges with really trying to tell for sure if a patient has a normal wedge as group 1 or if someone with a number of risk factors for left ventricular diastolic dysfunction, if we might be missing them doing a right heart catheterization after an overnight fast and they might be a little bit dry, and so, can you comment on the role of a fluid challenge?

Dr. Channick:
Yeah, I think it does have a role, although I have to be honest in saying it's rare that I feel it's necessary to do a fluid challenge. If I have this patient like I described with left atrial enlargement, older patient, and they have a wedge pressure of 14 or 15, I mean, I know what's going to happen when I give him fluid, but if you want to unmask it, give him fluid, sometimes we actually—this is sort of not evidence-based—but may do like a vasodilator test with NO and see if the wedge pressure goes up because that may actually inform treatment in some of these people where you're considering, let's say, silden-PAH therapy who have borderline wedge pressures. If you give them NO and you see the wedge shoot up and you see the wave, well, you've unmasked the patient with group 2 PH and may avoid treating him.

Dr. McLaughlin:
Yeah, I have had the same experience. Well, there are a lot of questions about right heart catheterizations, and hopefully, we'll have time to come back to more of them during the question and answer period, but I just want to make sure we get through the rest of the presentation.

Probably everyone has seen this slide about 600 times. I think it's a really informative slide. These are data or a table from the 2015 ERS/ESC guidelines that goes through the risk assessment of a patient with pulmonary hypertension or pulmonary arterial hypertension, and some of these have data behind them, mostly retrospective data; some of them are just things that we know make sense, like the progression of symptoms. There's no data behind that, but we've all seen this time and time again. And so the table from the ERS/ESC guidelines separated some of these factors out into low risk, like the expected 12-month mortality would be less than 5%, intermediate risk where the expected 12-month mortality would be between 5% and 10%, and high risk where you expect the 1-year mortality to be greater than 10%.

So the things that we know are important prognostic indicators are really how is the right ventricle functioning. If the patient has clinical signs of right ventricular failure on exam, that's a very high-risk feature. If their symptoms are progressing rapidly, we know those patients tend to just continue to go down so quickly.

Syncope is a really important symptom. Syncope often happens in pulmonary arterial hypertension patients with exertion, and it's often a result of just inadequate perfusion to the brain with exertion. You just can't get the blood flow through that high resistance in the lung, very much like with a syncope that aortic stenosis patients have. They can't perfuse their brain with exertion, and that really suggests advanced disease and pulmonary hypertension.

Functional class… You know, people criticize functional class right and left. It's so variable. It's so subjective. What Rich may call a 2, I may call a 3. But in registry after registry and trial after trial, it has important prognostic implications, so obviously functional class 4 patients have a high mortality. Similarly, with a 6-minute hall walk—it's a crude test, it gets a lot of criticism— but at registry after registry and trial after trial, it demonstrates it's important in terms of prognosis.

Cardiopulmonary exercise testing is not used quite as much, but there are also some data suggesting important cutpoints for the peak VO2 and the $VE/VC0_2$. Natriuretic peptides are important. They are prognostic. They represent, really, right ventricular failure stretch on the heart, and so there are some cutpoints listed there.

Imaging, I just don't think we've done as good of a job with imaging as I would like to see in our papers, really because there is not widespread use of MRI, which has some precise data points. On the other hand, echo, quite often they are reported as qualitative, and there's a lot of variability, and so we just don't have a lot of data looking at fractional area change or other indicators of right ventricular function. So, if you look at the literature, the 2 that are important and have been studied in registries include right atrial area and the presence of a pericardial effusion.

And then as Rich and I were just talking about, the hemodynamics that are most important, really it's not the pulmonary pressure. In fact, sometimes, as patients get sicker and the cardiac output goes down, so does the pulmonary artery pressure. Really what matters is the function of the right ventricle, as we've discussed: right atrial pressure, cardiac index and mixed venous oxygenation.

So, with that as a background, there are a number of risk assessment tools. Rich, do you want to start walking us through some of those?

Dr. Channick:
Yeah, absolutely. We don't have a lot of time, so we're not going to get into great detail. This has been, I'd say, a fairly recent advance in our knowledge in PH, that having a structured risk assessment really can help determine prognosis and help guide your therapy, and I think there are some very strong data to support that. And there are different tools, as Val alluded to. There's what's called the REVEAL Calculator 2.0, and you can see that laid out here where you can take a number of parameters, underlying diagnosis, demographics, and then modifiable things like functional class, hospitalizations, and one can determine a score, a risk score, that can be used not just at baseline but as well as in follow-up. And if you look here at the various components of the REVEAL Risk Calculator, there is nothing here that's surprising, per se, but it's nice to be able to, in a very discriminatory way, prognosticate at various stages in treatment using a lot of the parameters that Val has already alluded to. This is accessible and can be done in clinic, as I said, and a pretty powerful tool.

In addition—and this all came out a couple years ago—there are a few European-based registries that have come up with prognostic or risk assessment scores: the Swedish registry, French registry, and the COMPERA registry, and you can see here, without getting into all the details, that these were fairly similar. There were a little bit differences in what patients were actually included in those registries,

but not to get into details too much, they all basically showed very similar findings, that if you risk-assessed a patient using, again, commonly used parameters—BNP, functional class, 6-minute walk distance, in some cases hemodynamics—you could prognosticate pretty accurately in a patient with low, intermediate and high risk.

I would point out one thing here is that we are really talking about survival prognosis here, so you have to keep that in mind. There are other things that we want to know about a patient's clinical course, but if you want to predict survival, put a patient at low risk for a good long-term survival using these scores and, as you'll hear at the end, treating to get a patient to low risk.

I use a fairly simple French registry assessment in patients. We get BNPs, 6-minute walk and functional assessment at every visit. Cath we use at intervals to give a risk assessment. How about you, Val? I mean, do you have a structured risk assessment for all your patients as recommended?

Dr. McLaughlin:
Yeah, Rich, there are so many ways to do it, and I think one of the most important messages is just do it, that you have to do risk assessment with every clinic visit. I also love the noninvasive French. I do that every single time I'm seeing a patient anyway, right? It's functional class. I'm always talking to them, always assessing their functional class. Hall walk, we do that with just about every visit for just about every patient, and then labs, a BNP or NT-proBNP, we do that at every visit too, so it's really easy to do that, and we do that pretty frequently. You can get tricked sometimes. For me, it's the younger patient who functions really well despite a bad RV that's going to look better than they really are with that. And another one that I think is going to be really interesting—and you're going to talk about it to some extent—is the newer versions of REVEAL or REVEAL 2.0 Lite, which is very much like the noninvasive French but with vital signs and a serum creatinine or GFR added in, so I'm really looking forward to see how that functions in practice.

Dr. Channick:
Yeah, absolutely. I think it's really good. And then this slide just shows that… And this is really a critical point. It's really the follow-up assessment that's key, and we tell that to all of our patients. We can't prognosticate at baseline because we really don't know how they are going to respond. Hopefully, they respond well to the treatment regimen. So it's really the follow-up assessment that in some ways is more important. Another way to say that is I tell the patients, "I don't know how you're going to do it until I see how you do," and that's, I think, a really critical point. And you can see this here. The follow-up assessments really help discriminate prognosis.

So, again, the message that we're giving is that patients do need to be assessed at every visit, as Val said. You need to have some structured assessments. And even in our recommendations from the World Symposium that both Val and I were involved in, it says very clearly, structured or risk assessment is critical and recommended. It doesn't specify which particular one, but you need to have a system.

So with that I'll turn it back over to Val, who will get in and sort of dig into the therapies.

Dr. McLaughlin:
Yeah, thanks, Rich. That was a great overview of risk assessment, which I agree is so critically important. So the therapies that we have… and we have a slide here that shows the 3 pathways that we can currently target. And every time I show a slide like this, I always start out by emphasizing that we show these 3 pathways because we understand them really well and because we have agents that target these 3 pathways so we can actually exploit the abnormalities here to treat a patient, but I always emphasize that this is just the tip of the iceberg. There are so many other dysfunctional pathways in pulmonary hypertension, and hopefully, over time, we will be able to study more of them and have agents that can target growth factors, inflammation, and many other pathways that we don't currently target. Just think of this as the tip of the iceberg, and hopefully, in a few years, Rich and I will be back speaking with you and there will be 4 or 5 or 6 pathways here, but for now, this is what we have.

And starting from the left we have the endothelin pathway, and the problem here is there is too much endothelin-1, which then targets the endothelin A and B receptors on smooth muscle cells, and that causes vasoconstriction and ultimately cellular proliferation. And we have oral agents that can block those endothelin receptors.

The middle pathway is the nitric oxide pathway, and the problem here is there is a reduction in nitric oxide synthase, which is required to convert L-arginine into nitric oxide, which then works via the cyclic GMP pathway to result in vasodilatation, and ultimately, this has antiproliferative effects. And we can target this pathway 2 ways. We can block PDE-5, which inhibits the degradation of cyclic GMP, but we also have direct sGC stimulators, riociguat, which can stimulate sGC really independent of any nitric oxide production.

And then on the far right is the prostacyclin pathway. That's the very first pathway that we ever had for pulmonary arterial hypertension. And the problem here is there's not enough prostacyclin synthase, which is required to convert arachidonic acid into prostacyclin I2, and that works via the cyclic AMP pathway to result in vasodilatation, and ultimately, it inhibits cellular proliferation. And we have many ways of targeting this pathway. There are many different types of prostacyclin analogues which can be delivered IV, subQ, inhaled, and

orally, and then there's also an IP receptor agonist that can be delivered orally as well.

And so, over the years… And I think Rich and I have had a very exciting career to see so many agents FDA-approved for pulmonary hypertension. I think every single one of the agents on this slide has been approved during the course of our careers, so that's been very exciting. There are 3 FDA-approved oral endothelin receptor antagonists targeting the NO pathway. There are 2 PDE-5 inhibitors approved and then the sGC stimulator, riociguat. There are a number of prostacyclin analogues, as I said: IV, subQ, inhaled and oral, so it's been a really exciting development time.

So let's start out. We'll go through some of these. I think probably most of you are aware of many of them, but we'll just summarize some of the highlights. I'll start with the endothelin receptor antagonist, as I mentioned, that the stimulation of those receptors causes proliferation, hypertrophy and vasoconstriction and also fibrosis and inflammation, and we have a number of ERAs that can target this pathway. It's important to remember that all of these are teratogenetic, and, of course, we know patients with pulmonary arterial hypertension should not be getting pregnant anyway, but we have to counsel our patients that they need to use 2 methods of contraception and have monthly pregnancy tests.

The agents that we have available are listed on this slide. There is bosentan, which is really the first oral agent that we had available for pulmonary arterial hypertension, and this agent still requires LFT monitoring. The subsequent agents, macitentan and ambrisentan, no longer require LFT monitoring, but they still require pregnancy testing and are still distributed by a specialty pharmacy because of the risk evaluation and mitigation system that they need to be distributed under because of those side effects. Bosentan and ambrisentan were initially FDA-approved on shorter-term studies that demonstrated an improvement in 6-minute hall walk, and macitentan was approved based on the larger SERAPHIN study, which looked at some time to morbidity and mortality.

Then we move to the PDE-5 inhibitors and sGC stimulator. Rich, do you want to...

Dr. Channick:
Sure.

Dr. McLaughlin:
I'm sorry, that's still me. So the…

Dr. Channick:
No, I think—I think that is me. I think it is me.

Dr. McLaughlin:
Okay, go ahead. Sorry.

Dr. Channick:
Yeah. See, we're a good team. Yeah, so if you look at the nitric oxide pathway, it's obviously a very important signaling pathway in smooth muscle cell tone and in vascular relaxation and clearly is impacted in pulmonary hypertension, and so it really makes sense to address that pathway, and we can do it now 2 ways. We have PDE-5 inhibitors that obviously block the breakdown of cyclic GMP, as Val alluded to, and there are 2 of those, sildenafil and tadalafil. They both have been shown to have benefit, also relatively short-term trials, sort of the older way we did trials with the 12- or 16-week effect on exercise capacity, and both showed benefit. In practice sometimes we'll use one versus the other. Tadalafil is nice because it's longer-acting and seems to give a nice effect. Sildenafil we may use in patients who may be a little more fragile that we may start a lower dose and less frequently. Different patients seem to tolerate different ones better between the 2 PDE-5 inhibitors is one way to say it. Riociguat is unique, as Val alluded to, in that it's an oral soluble guanylate cyclase stimulator, so it works in a different way by directly increasing cyclic GMP levels independent of nitric oxide, and that, I think, makes it a nice alternative in some cases to PDE-5 inhibitors. And we should warn you, and you probably already know this, that any other nitrates, including for coronary disease, angina, PDE-5 inhibitors for any reason cannot be used with riociguat, and it also is a category X for pregnancy, and so approved under the tradename Adempas. So those are the... That's the nitric oxide pathway in terms of FDA approval.

I guess I can mention the REMS program, and we've alluded to this, but this is a Risk Evaluation Mitigation Strategy. You can see here that all females must enroll. Females must not be pregnant, and it talks about monthly pregnancy testing for these drugs. And healthcare providers themselves must enroll in the program as well as these things being closed distribution, only a limited number of pharmacies.

So now we'll person to the prostacyclins, and we'll have Val run through those.

Dr. McLaughlin:
Yeah, and the prostacyclins, we know this pathway the best. This was the very first pathway that we had to target pulmonary arterial

hypertension. In 1995, IV epoprostenol was approved, and so we have a great deal of experience with that. We also have treprostinil, which can be delivered in a number of ways: continuous IV, continuous subQ, intermittent inhaled or orally either twice or 3 times a day. We also have iloprost, which is delivered inhaled. And selexipag, the mechanism of action here is a little different. This is the IP receptor agonist, which is an oral, twice-daily agent.

Let's talk a little bit about oral treprostinil. This is FDA-approved. Actually, the FREEDOM-EV trial was recently released which demonstrated an improvement in outcomes when using this on top of just one other oral background therapy. This one can be a little tough to use. Patients have a number of side effects, and so you have to start at a low dose and go slowly and make sure that the patients take it with food, but they have these prostacyclin side effects: headache, diarrhea, nausea, flushing. All the prostacyclins have those, but sometimes the GI side effects are a little bit more prominent with oral treprostinil and really requires really a collaborative approach. I'm so grateful for my nurses who spend really a great deal of time on the phone with our patients in general and particularly titrating prostacyclin therapies and managing those side effects.

Prostacyclins can also be used inhaled, or treprostinil could also be used inhaled. This was studied in the TRIUMPH study. And again, you need to be taught by a specialty pharmacy nurse, and the dose needs to be increased gradually. This can have the typical prostacyclin side effects, also can have cough and throat irritation because of the delivery mechanism, but it's a good therapy in appropriately selected patients.

Inhaled ILOPROST, another prostacyclin-inhaled therapy, you have to take it a little bit more frequently than inhaled treprostinil. Side effects are really quite similar.

Selexipag, I think we were all very excited about this agent based on the GRIPHON study. It's been so nice to move from these short-term 6-minute hall walk trials to these longer-term morbidity and mortality trials, and that was the GRIPHON study that looked at selexipag, the largest study that's ever been done in patients with pulmonary arterial hypertension, but this is another tough drug to use. The side effects are similar to IV, but the dose titration really needs—the patients need some handholding, and we really need our expert nurses to help manage those side effects.

And then the IV epoprostenol, this is the one that's been on the market the longest. I think we have a long history with this therapy. Fifteen years ago, 20 years ago when we didn't have any other choice, everyone went on this therapy, and now there are many other choices, and so mostly this is used in patients with the most advanced symptoms, the functional class late 3, 4 patients or the patients who are not improving when we start other oral therapies first. The patients need to be taught the techniques of sterile preparation of the medication, operation of the ambulatory infusion pump and care of the Hickman catheter. There is now a room temperature-stable formulation, Veletri, so that they don't need the ice packs. And sometimes we can even get them premixed cassettes, and that's actually a big quality of life improvement for patients.

And then treprostinil can be delivered both IV and subQ. SubQ you don't have the risk of IV line infections of bacteremia, but sometimes it causes pain at the site of the subcutaneous infusion, and there's really no way to predict this. In some patients it's a little, and they can tolerate it, and they would much rather be on that than an IV therapy, and in other patients the pain is so severe that they say, "I'd rather be on the IV therapy," and you just don't know. Here again is another important area where our specialty nurses are so involved in the care of these patients.

They are looking at an implantable pump for IV treprostinil. There are a handful centers that were in the clinical trial that have some patients on that pump, but it's not widely available yet. It mitigates the risk or really eliminates the risk of central line sepsis, but the patients need to return to the center to fill the pump.

And I guess, Rich, I think that this is a nice opportunity, as I've tried to emphasize, that the team approach and the collaboration with our nurses who really spend so much time walking the patients through these therapies would... I just was wondering what your experience has been like with managing these patients.

Dr. Channick:
Yeah, you said it beautifully, Val. I mean, the key to successful therapy with prostacyclins is understanding how we titrate, understanding side effects, understanding how to get patients through those side effects, and there are no shortcuts to that. As you said, they need some handholding, but the success of the drug, of any of these drugs, depends on that. They are all the same in that respect in the prostacyclin pathway, that the drugs are titrated from very low doses, in some cases very high doses, and everything in between, and to do that, the only way you can suggest we do that is if the patient understands what to expect and that they have a lot of support, whether it's with the mixing of the drug, dealing with the site pain if it's subQ, dealing with the other prostacyclin side effects, and then for the clinician, the healthcare provider, to understand when is enough and when is too much with the drug, and that requires some experience in terms of what is an acceptable prostacyclin side effect and what are the best ways to manage those side effects.

Dr. McLaughlin:
Rich, I think that's a really great point, and the way I describe that to patients is we need to balance the symptoms of pulmonary hypertension with the side effects of the drug, and that's a shared decision-making. That's an experienced physician talking with the patient and sorting out their symptoms and the impact that the side effects have on their quality of life.

Dr. Channick:
Yeah, absolutely. Again, we say that you're going to have some side effect with these prostacyclins, and if you have no side effects, you're probably not getting enough of it, but we don't want them to affect your life, so we want them manageable, so it's manageable side effects that we're really looking for in some ways.

Dr. McLaughlin:
Great. Rich, you and I have been doing this for a long time. I referenced that 20 years ago we only had IV epoprostenol and we would start a patient on one therapy. Our treatment strategy has evolved so much over time.

Dr. Channick:
Yeah, absolutely it has, and that's, again... We're looking for new drugs, as Val said, and there are new targets and new pathways, an extraordinarily exciting time. But even with the treatments that we have now, how do we use them together? It certainly makes sense that if we have drugs that work in different pathways, does combining them actually work? And so, early on in studies that Val led and I've been involved in, we looked at sequential combination therapy, so adding drug B to drug A and adding drug C to drug AB and B, and that has shown benefit. Big studies: Val alluded to the SERAPHIN study with macitentan; there's the GRIPHON study with selexipag. These are what we call sequential combination studies that showed benefit. But things evolved even more, I would say, in that our current paradigm in many cases is actually starting upfront combination therapy, so drugs A and B and maybe drug C all starting initially, and we have data now emerging that that's an effective approach.

The AMBITION trial, the slide shown here, was really the first one that looked at a combination of 2 drugs, an ERA and a PDE-5 inhibitor, as upfront combination therapy compared to either one alone, as you can see here, and this was really the first large, upfront combination study that looked at a morbidity and mortality endpoint shown as clinical worsening or what we call inadequate long-term clinical response. It wasn't just enough the combination kept them from getting worse but that they actually reached an adequate clinical status, and I think that's an important concept in clinical trials in PH is that getting patients to a good profile is important, and certainly keeping them out of the hospital. So this is the classic composite endpoint, and that was certainly shown to have significant benefit. This was upfront combination therapy in the AMBITION trial showing a 49% risk reduction of not reaching that endpoint of adequate or good clinical response, and so that's, again, really led to the evolving paradigm I would say. And this is just again showing a little bit more data on reducing the risk of hospitalization for PAH and showing, again, similar benefits with the combination of the 2 drugs.

Dr. McLaughlin:
So, Rich, if I could just pause here to interject.

Dr. Channick:
Absolutely.

Dr. McLaughlin:
I think that's a really important point to stress. A hospitalization for PAH is bad. Once you get hospitalized, your subsequent mortality goes up, and there has been some important data from that published. Actually, even in the REVEAL registry they learned that as well, and so REVEAL 2.0 actually added a hospitalization to the risk factor, so I think it's really important to underscore that a hospitalization in and of itself is a high-risk issue.

Dr. Channick:
Yeah, I agree, and this is something that's emerged not just in AMBITION but in other trials as well that both of us have been involved in. With macitentan, the SERAPHIN trial, it was a secondary endpoint, but we published a paper on 50% reduction in hospitalization with macitentan, PAH hospitalization. As you know, in the GRIPHON trial, hospitalization was also part of the primary endpoint and seemed to drive a fair amount of that. The benefit of the selexipag was the reduction in hospitalization in the treated group.

Dr. McLaughlin:
Yeah, so I…

Dr. Channick:
Yeah.

Dr. McLaughlin:

Yeah.

Dr. Channick:
So a very important endpoint. There are still patients, and lung transplantation has been performed for at least a few decades for patients with PAH. It's evolved, but for the most part, bilateral lung transplantation still has a role. I think it still clearly has a role. I think the nice thing is that we have these medical therapies that many patients do very well on for many years and don't need a lung transplantation, but there are still our patients who will need that. Survival is not the best with lung transplantation, although we certainly have patients who do very, very well after bilateral lung transplantation, and so I think what we're recommending is that patients who do remain intermediate or high-risk—and this came from the 6th World Symposium recommendations—should be referred for lung transplant evaluation.

Dr. McLaughlin:
So, Rich—

Dr. Channick:
Yeah.

Dr. McLaughlin:
—over the years we've developed new ways of allocating lungs. When we first started doing this, it is just time on the list, and we often just referred patients so they could accrue time. How do you think the lung allocation score has changed how we refer patients for lung transplant or how many of our patients get to lung transplant over the recent years?

Dr. Channick:
Yeah, I think it's made a huge difference. I think it's actually been a real improvement in how we do it, and I remember the days where it was a dilemma. You had to put people on very, very early knowing they might wait years for the transplant, and you had to hope that you could keep them going until the transplant, and it was really a true first come, first served, the earlier they got on the list. They were worked their way up the list for their blood type and size until they got the call. In addition, you might have the opposite problem where the patient is getting called, and they are doing really, really well, and then they'd have to deny the transplant, and then they would be off the list or at the bottom of the list, so it was a real mess, but now with the LAS system, although it's not perfect… because patients with lung disease are very varied. They have cystic fibrosis, emphysema, pulmonary hypertension, so the prognostic scores are very different and what goes into them. But having said that, I find it to have been a drastic improvement in that our patients now wait… By the time they get on the list, they have a much shorter waiting time. Have you seen the same thing?

Dr. McLaughlin:

Yeah, definitely. And then we can also be a little bit more reserved about doing all the transplant workup in everybody, right? Because we only do it in those patients who remain quite symptomatic despite medical therapy.

Dr. Channick:
Yeah, absolutely, yeah.

Dr. McLaughlin:
Yeah. We talked about some of the PAH-specific therapies, and let's just spend a short bit of time talking about some of the other supportive therapies that are important. Way back when anticoagulation was pretty standardly used, it was really based on observational studies and registries before we had any specific PAH therapy, and more recent registries in patients who are on our agents have demonstrated really no improvement with anticoagulation, and some of our patients, such as those with scleroderma and high risk of GI bleeding, could actually be harmed, and so I don't think we use... Actually, we've taken off anticoagulation in many of our patients. Rich, have you done the same?

Dr. Channick:
Yeah, I mean, for a patient with true group 1 PAH, it's very rare we put them on anticoagulation nowadays. I mean, there may be exceptions. If somebody has an indwelling catheter and they have a large interatrial communication and we worry about paradoxical embolism or things like that, we may have them on some anticoagulation, but not that many.

Dr. McLaughlin:
Yeah, that's a great example. I think something that we don't pay enough attention to is the need for supplemental oxygen. Our patients get hypoxic, really not just at rest but also at night, with exertion, with altitude, and hypoxia is a further vasoconstrictor, so we want to try to make sure we address that and use supplemental oxygen when appropriate. There aren't studies with diuretics—I'm sure there never will be—but many of our patients need diuretics. They are in right heart failure, the right ventricle is on a bad place on the

Frank-Starling curve, and if we can optimize their volume status and take some of that stress off the right ventricle, they do better.

Obviously, you need to monitor electrolytes, creatinine. I think it's also important to remember that hypotension is not a reason not to use diuretics. In fact, some of our sickest patients who come in with hypotension, your reflex is to give them fluids because they are hypotensive, but if they are in bad right heart failure, that's really only going to make them worse, so it's important to remember volume status. And I think patients and other physicians, nobody really wants to deal with volume. It's hard work, it's frequent monitoring, the patients sometimes give you pushback about taking their diuretics because they don't want to have to be going to the bathroom that much, they really struggle with sodium restriction, but it's a really important part of the care, and it's another place where I think our nursing staff is really integral. I can't tell you, I walk by my nurses area, and I hear them talking to a patient and literally asking, "Tell me what you ate yesterday," and the patient thinks that they are not getting too much salt because they don't pick up a salt shaker, and they don't really realize how much is in McDonald's, so I think that's a really important aspect of their care as well that is sometimes overlooked.

I really want to put in a plug for physical activity or supervised rehab. Of course you want to get patients on therapy and feeling better, but once you do, it's important to encourage them to exercise. There are some studies that show pulmonary rehab improves 6-minute hall walk as much as any of our drug therapies do, so it's really critical, and these days with activity trackers and the like, you have something objective to measure. I've gotten some patients hooked on Fitbits or other activity trackers that every time they come in they tell me what their average step count has been, so I think that's a great motivator. As we've mentioned, our patients with pulmonary arterial hypertension should not get pregnant. There is a high risk of both maternal and fetal mortality, and so we need to counsel them on contraception, and that's a really important issue. So many of these patients are young women, so it's really important. And then the psychological support is really a hard issue to deal with. A very high proportion of these patients have depression or anxiety. And it's not just the patient, it affects the family too, so it's important to think wholistically about some of these other issues that can affect patients.

Kind of wrapping it all up, moving to the algorithm—and this was from the last World Symposium—and starting at the top, it's important to make sure that the diagnosis of PAH is confirmed by right heart catheterization. The general and supportive measures that I just reviewed are something to consider. It's important to do acute vasoreactivity testing in those groups that may have that very robust response in calcium channel blockers. If they meet the criteria, which is a reduction in mean pulmonary artery pressure by more than 10 mm to a mean pulmonary artery pressure of less than 40, if they meet those criteria on an acute vasodilator exam, they can be given calcium channel blockers, and then they need to be followed. And the patients who are going to do well long term on calcium channel blockers are those patients who improve to functional class 1 or 2 without the need of other therapy. I generally… Even if the patient tells me they are functional class 1 or 2, this is a population that I will routinely repeat a right heart cath on in 6 months, 6- to 12-month time frame, because if they are really a calcium channel blocker responder, you expect to see pretty much normalization of their hemodynamics. Do you approach that group similarly, Rich?

Dr. Channick:
Yeah, I tell the patient, "You are unlikely to get this disease, but you are really lucky to be in this group because very few of our patients are highly vasoreactive," and because of that—and they are often young people, young women—I say, "Our goal is to get you normal." These may be women in their 30s, and you say, "I want to see a normal echo. I want to see normal hemodynamics." And so we're pretty aggressive because they are in that very fortunate subgroup.

Dr. McLaughlin:
Right. For the vast majority of patients who aren't those privileged calcium channel blocker responders, we go to the risk assessment, and Rich very eloquently reviewed that. And whatever risk assessment method you use, it doesn't matter; you just gotta do it. If they are high-risk—and they could be high-risk because the REVEAL score is 15 or because they are functional class 4, they are all in the red zone on ERS/ESC or they meet none of the French parameters—whatever reason that is that they are in the high risk, most of us would recommend upfront combination therapy that includes a parenteral prostacyclin therapy. It's really important to be aggressive about those patients. They have a very high mortality in the ensuing year or even less. Now, fortunately, I think that's a pretty small proportion of the patients that we see, but it's important to remember that there are some patients who need IV therapy really right out of the gate.

For the majority of the rest of the patients who are at low or intermediate risk, we use upfront oral combination therapy generally with an ERA and PDE-5. That's the first step, but honestly, it's not the most important step. The most important step is reassessing that patient, reassessing them after 3 to 6 months of therapy. I tend to go more towards 3 these days and see if they meet the low-risk status. If they are low-risk, that's great. What you've done has been working. You can feel comfortable continuing them on that with continued reevaluations. But if what you did the first time doesn't work, if they are still at intermediate or high risk, you have to do something different, and that something different could be adding a third agent, it could be switching to a more aggressive prostacyclin if

you started them on a prostacyclin, but you have to do something different and try to drive them down into low risk, and so I think that that constant reassessment really for the rest of the patient's life is something that is important.

Rich, any comments on the algorithm?

Dr. Channick:
No. I mean, I was involved in developing this, and again, we purposely kept it broad and focused on the principles of management rather than specific agents, and I think that's really how we've evolved now that we have so many effective agents, that we are really focusing on treatment strategies and combination therapy, when to use combination, when to reassess, when to add more therapy.

Dr. McLaughlin:
Rich, always a pleasure to work with you. Thank you so much, and thank you to the audience. I'll let you close with any final comments, Rich.

Dr. Channick:
Yeah, again, so many good questions. I mean, this is obviously a sophisticated audience based on the questions they're asking. Reach out to us offline if you ever want to discuss. I don't think either of us ever gets tired of talking about PAH amazingly, but we don't, and so we're always happy to discuss these things in detail with interested people.

Dr. McLaughlin:
Great. Thank you to everyone.

Dr. Channick:
Thanks for your attention.

Announcer:
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