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Maximizing PH Care Using Risk Assessment to Improve Outcomes

Announcer:
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Dr. McLaughlin:
Hello, and welcome to this program on "Maximizing PH Care Using Risk Assessments to Improve Outcomes". I'm Valerie McLaughlin, Director of the Pulmonary Hypertension Program at the University of Michigan. And I'm so glad you can join me for this.

So why is formal risk assessment critical to effective treatment of pulmonary hypertension? Well, we've learned so much about risk assessment over the past decade or so. We know it's really critical in many chronic diseases and through many databases, we've learned that comprehensive patient assessment in PAH allows us to determine a patient's prognosis, monitor their disease progression, and their response to therapy. It really helps us make treatment decisions. It's become a critical part of the ESCERS guidelines for the care of patients with pulmonary hypertension. And those guidelines recommend that risk assessment be conducted regularly every three to six months in stable patients. And it's really critical that the risk assessment include multiple parameters to evaluate disease progression and the patient response to therapy. So risk assessment should include a range of clinical hemodynamic and exercise parameters. And we really look at all of these together. There's no one variable that we rely on to provide definitive prognostic information.

So we know that pulmonary hypertension is a complex disease and often actually the patients have really advanced symptoms by the time they present to us. There are a number of factors that influence the development of pulmonary hypertension, including genetic and genomic factors, but also environmental factors as well. And we know early in the course of disease, the pulmonary pressures go up and the patient may not be very symptomatic. And because the right ventricle is coping with those pressures, but at some point in time, the right ventricle becomes stressed by that high pulmonary vascular resistance. And it doesn't function as well. And the pulmonary pressures and pulmonary vascular resistance go up and ultimately the right ventricle becomes compromised, and it may even fail. So by the time the patient becomes symptomatic, the pulmonary vascular disease is really quite advanced. And the thing that causes patients to get sicker is not that the pulmonary pressures keep going up and up and up, it's that the right ventricle has trouble coping with that high resistance and the right ventricle fails. In fact, as the patient gets sicker, you might even see the pulmonary artery pressure decline because the right ventricle just can't generate enough output. We'd see this in left heart failure as well.

Now as I said, patients are often very advanced by the time they get diagnosed, even current day, most of the patients I see have functional class three symptoms at the time of diagnosis which is unfortunate because we know that the sicker they are when they get to us, the worst their outcomes are. So on this slide, our data from three different registries looking at baseline risk assessment and survival. The Swedish PAH register on the left and COMPERA on the far right use essentially the same methodology. They look at the variables from the ERSESP guidelines and really assign a score of one if it's low, two it's intermediate and three if it's high and then divide by the number of variables and round to the nearest integer to get low intermediate and high risk. And you can see in both of

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those registries, the patients at high risk depicted in red at the time of diagnosis have a much poorer prognosis than those at intermediate risk depicted in yellow or those at low risk depicted in green. Very, very similar results in those two databases. Now if you look in the middle, there's the French registry and they do things a little bit differently. They basically said our goals of being low risk include four parameters, one, to have functional class one or two symptoms, two, to have a six minute haul walk of greater than 440, three, to have a right pressure of less than eight, and four, to have a cardiac index of greater than 2.5. And if you meet all four of those variables, you can see in green, the prognosis is very good. That means you're less ill at the time of diagnosis. The blue is three variables, the red is two, the blue hashed is one and the gray is zero. And you can see that the prognosis gets worse the fewer variables you have or said another way, the prognosis gets worse, the higher risk that you are. So this is one of the reasons it's important to emphasize awareness, emphasize early diagnosis, and an early referral to a pH center, because we know that the more advanced you are at the time of diagnosis, the worse your prognosis is.

However, the good thing is that even if you have advanced symptoms or advanced risk at the time of diagnosis, you still have the opportunity to respond to medical therapy. And if you respond to medical therapy and if we can improve your risk status, then your prognosis improves. On this slide, you see those same three registries. And what we're looking at here is the patient's risk assessment at the time of their first follow up. So they were diagnosed, their risk was assessed, they were started on therapy, and now we're risk assessing them again on therapy. And the good thing is, is that if we can improve their risk on therapy, their prognosis is much better and it's consistent across all of these databases, but let's focus on the far left, on the Swedish PAH register. Cause I think this demonstrates it very, very nicely and is a little more simple to look at. So on the left, you see the same sort of risk assessment looking at the variables from the ERSESC and kind of adding their scores dividing by the number of variables measured and assessing whether or not they hit low risk status. And what you can see in the green line are the patients who presented at low risk and are still at low risk, stayed at low risk at the time of their follow up. And their subsequent prognosis is very good. But I call your attention to that lighter blue line on the top. These are patients who were not at low risk at the time of diagnosis, they were at intermediate or high risk at the time of diagnosis. And then with therapy, they improved to low risk. You can see that their subsequent five year survival is essentially the same as the patients who were at low risk and stayed at low risk. This is really critical, and this is one of the reasons our treatment algorithms are based on achieving low risk, because we know that no matter where you start, if we can get you to low risk, your prognosis is good. On the other hand, in the darker blue line, you see the patients who were at intermediate or high risk and stayed there. So the prognosis is not so good. And even worse are the patients who were at a better risk level and did response therapy and progressed and worsened to intermediate or high risk. And you can see their survival is very poor, 20% die within the subsequent year and more than half of them die within five years. And we won't go through the other two registries, but they're really very much the same. If we can improve to low risk, the prognosis is better.

So I hope this helps convince you that risk assessment to monitor prognosis and PAH is an important part of care. And included in this risk assessment are clinical functional exercise, non-invasive and sometimes invasive therapies, or invasive variables that all go into our risk calculators. Now there are a number of risk calculators available. There are different models, the French pulmonary hypertension registry uses those four variables or there is a less invasive way that swaps out NT-proBNP for the hemodynamics of right atrial pressure and cardiac index. There's pH connection, there's COMPERA and Swedish which we've talked a little bit about, which are really based on the ERSESC guidelines. There's a Scottish score. And then of course there's the reveal risk equations, reveal is a very large US based registry that has created a calculator and a number of equations and including more recently, a less complex equation that only has six variables reveal like two.

So, how we categorize risk of mortality must dictate how we treat our PAH patients, and we need to assess risk regularly, but there are some limitations to our risk stratification scores. And this is a depiction that really, I think kind of accurately describes how our patients fall. And of course, those in red, the highest risk they need aggressive therapy, including combination therapy with a parenteral prostacyclin, small number of our patients are at low risk at the time of diagnosis. And some of those may be appropriate for monotherapy, but the widest majority of our patients are at intermediate risk. And in fact, if you look at registries about 70% of patients, fall into the intermediate risk category. So, I would submit if your risk stratification tool, put 70% in the same bucket, then maybe it's not as good as we would like. Maybe there are refinements to that. And even when I think about intermediate risk, I think in my own mind, I think low intermediate, high intermediate, I mean we treat patients a little bit differently, depending on where they fall.

So, these earlier iterations of risk assessment, had patients fall into three categories, low, intermediate, or high but of course with 70% falling into that intermediate risk, we think that there's an opportunity for improvement. And we should consider that initial treatment strategies, may vary within that intermediate risk group, reflecting the range of the disease severity. Now, despite this, if we look at registries less than half of our patients, even in the very experienced hands of some of these investigators, less than half of our patients, achieve the goal of low-risk status. And that really makes us think about risk assessment, how we can be more aggressive and how we can be more precise with it, because the success or failure of our overall PAH treatment, depends on the initial risk treatment

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strategy and how we follow that up.

So, here is the algorithm from the 6th World Symposium and this is really a simplified version here. And of course, any algorithm starts with the correct diagnosis, referral to a PAH center, a place that has experience. We always talk about some of the general and supportive measures, talking about exercise, sodium, volume, oxygen, those sorts of things. It's important to do an acute vasoreactivity test at the time of the initial right heart catheterization, particularly for those patients with idiopathic heritable and drug and toxin induced pulmonary arterial hypertension, because a small proportion of those, probably only about 6% will have a very robust response to that acute vasodilator testing and be candidates for calcium channel blocker therapy, which is obviously a very simple therapy that can improve prognosis in such patients. But it's really important to remember that the response is very specific, a reduction in mean pulmonary artery pressure of at least 10 millimeters of mercury to a mean of less than 40 in the setting of a stable cardiac output, a normal cardiac output that does not go down with the vasoreactivity testing. So, that's an acute response, but really what determines the long-term response is how they clinically respond to calcium channel blockers. And those who are going to respond long-term, improve to functional class one or two symptoms, without the need for additional therapy. So, those patients are a very small group of patients, but it's really important to identify them, because a very simple, well tolerated inexpensive therapy, can make a big difference in their lives. So, for the vast majority of patients who are not vasoreactivity positive, we decide their therapy based on their risk. And so, if they are at high risk, I'm on the far right here, if they are at high risk, be it because they're having syncope or they're in florid right heart failure or the right atrial pressure is 25 and that cardiac index is 1.7. If they're that high-risk patient, they need aggressive therapy that is combination therapy with a parenteral prostacyclin. That's really, really critical. And sometimes we even talk about lung transplantation to those patients at the time of diagnosis. If they are not vasoreactivity, but they are not at high risk, they're in the intermediate risk or sometimes even the low-risk range. We generally start with oral combination therapy. There's lots of great data for ERAPD five combination therapy at the time of diagnosis, there is a potential role for initial monotherapy in a subset of patients, perhaps those patients that don't clearly fit, into the clinical trial entry criteria for combination therapy or those with a lot of risk factors for diastolic heart failure that you're a bit worried about, but most of the patients now start on, dual oral combination therapy. So, we spend a lot of time talking about that middle section of the treatment algorithm. But what I think is the most important is that last section of the treatment algorithm and that really highlights the structure to follow up. So, whatever decision you made about therapy in that middle section, you need to reevaluate within three to six months and honestly, I really lean towards the three month period now. We need to do a structured follow up. We need to use one of the objective risk assessment tools and determine their risk. And if the decision you made in the middle section of the algorithm, if the patient responds, they're doing well, they meet the low-risk criteria. That's great. You don't need to change their therapy at all. You just continue structured follow up. If they are not meeting those low-risk criteria, if they're still at intermediate or high risk, you need to do something different and that something different, could be adding another therapy, adding a second therapy if you started with one, adding a third therapy if you started with two, going to more aggressive prostacyclin. The point is you need to escalate therapy and continue to risk assess them to try to get them into the low-risk category.

Now, unfortunately, despite our best efforts, we don't get a lot of patients into the low-risk category or certainly not as many as we would like. This is a very nice paper from an Italian group, where they look at the risk at baseline and then the risk at first follow up, using the European Society of Cardiology, ERS/ESC guideline method on the left and REVEAL 2.0 on the right. So, what you see on the left is you have the patients, who fell into low, intermediate or high risk at the time of diagnosis and on the bar graph in the colors, you can see what they were at time of their first follow up. So, green is low. Yellow is intermediate and red is high. And if we just look in the middle bar, those are the patients who are at intermediate risk. At the time of diagnosis, you can see that we get less than half of those patients to low risk with upfront double combination therapy. And the majority are still at intermediate risk. And even if you have worsened to high risk, I think it's also important to look at the high-risk category at the time of diagnosis. So, the bar on the far right of the graph on the left and you can see that of the high-risk patients that were started on double oral combination therapy, we don't get any of them to low risk. We get about 60% of them to intermediate risk and about 40% of them stay at high risk. So, while dual upfront combination therapy, has really revolutionized the care of PAH, you can see that the majority of patients, don't get to low risk with just that therapy and on the right, you see a very similar situation for risk stratification using the REVEAL registry. Again, if we look at the middle bar, the ones with a reveal risk score of seven to eight, which would be intermediate risk, we can get about half of them to low risk and the remainder are intermediate and high. And again, if you look at those with a high REVEAL risk score greater than eight on the bar on the far right, we can see that despite dual upfront combination therapy, we don't get any of those patients to the low-risk status. We improve about half of them to intermediate.

Now, I want to focus on this paper from the French registry. This was a recent publication from the French registry that basically just said, let's look at the initial treatment strategy, how the physicians decided to treat these patients and what the outcome was. And the graph on the left, looks at the patients who were at high risk at the time of diagnosis. And the graph on the right looks at patients who were at intermediate risk at the time of diagnosis and the red line signifies that their initial treatment, was upfront combination therapy that generally included a parenteral prostacyclin. In fact, it always included a parenteral prostacyclin, and you can see in the high risk

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patients, the sickest of the sick, there was a marked survival benefit in patients who were treated with combination therapy with three drugs, with the parenteral prostacyclin, compared to patients who were treated with dual or monotherapy. And we're not surprised by that, right? The guidelines all say high risk patients, need aggressive therapy, but I think what's even more impressive is on the right, the intermediate risk patients. These are that 70% of patients in the intermediate risk group. And obviously there's some selection bias here, but the intermediate risk patients who are treated with combination therapy, triple combination with a prostacyclin, they did better than the intermediate risk patients that were treated with dual or monotherapy. I think that difference is pretty striking and that leads us to really reassess, how aggressively we treat patients and how frequently reassess them. And maybe even what that intermediate risk group does or what they're like.

And this graph, we call this the orange people chart. This graph is from an editorial that we wrote that went along with that paper. And it really highlights that there's a wide variety of patients in that intermediate risk group. And they're not all yellow. There are going to be some patients in that intermediate risk, who have some of the higher risk features that maybe they're more orange than yellow. And maybe it's those intermediate risk patients that did better with the parenteral prostacyclins, as part of triple therapy in the French registry. So, maybe at the time of baseline assessment and baseline choices, we shouldn't just say, all right high gets triple combination with parenteral prostanoids, low maybe you can get mono or maybe dual therapy and all the intermediates get dual therapy. Maybe there are some of the intermediates, who have enough highest risk features that they should be getting more aggressive therapy, that they should be getting, parenteral prostacyclin therapy from the onset. And I think that the other point is early reassessment, that we know that not all patients are going to respond. We saw in the Italian literature that less than half of these patients, are going to get to low risk. So, if they don't get to low risk, why wait six months? Why not reassess them a little bit sooner and try to get them into the low-risk status? And again, the patients in that intermediate risk group, may fall into different shades. They may not be all yellow. There may still be some patients with higher risk features who deserve more aggressive therapy.

So let's look at a new risk assessment model. Let's look at changing the intermediate risks here. So we've highlighted this already. In spite of advances and validation of PAH risk scoring methods, the discrimination characteristics are good, but they're not excellent and it remains uncertain what the best treatment strategy is for patients who remain in that intermediate risk group. And in fact, that intermediate risk group is a big group, 70%. And perhaps a more nuanced approach with a refined definition of intermediate risk may help us more in our treatment decisions. So to address the problem of the intermediate risk group, the COMPERA investigators suggested subdividing them into different levels, intermediate low and intermediate high. And this four-strata risk approach described by the COMPERA registry used a revised scoring system and cut points for the very important variables of hall walk, functional class, and NT-proBNP or BNP that may better define the risk groups. And so this analysis has been done in both COMPERA and then actually validated in the French pH registry.

So here are the results looking at the COMPERA approach to risk stratification. We have the three-level of risk on the top and then the four-level of risk on the bottom. So this is taking the French registry and using the old three-strata method of low, intermediate, or high and then taking this new approach that was defined in the COMPERA registry and applying it. So on the top, you see curves at baseline and at first follow-up, first reassessment, that show how low, intermediate, and high separate these curves. And on the bottom, you see low on top and what we now call intermediate-low in blue, intermediate-high in yellow, and high in red. And you see a nice separation of those curves and you see that intermediate risk group, there's different groups within that. You can see the difference between intermediate-low and intermediate-high. And this really correlates with mortality using Cox regressions. There was an increased risk of mortality in the first follow-up with increasing risk strata and you can see the three-strata method on the top and the four-strata method on the bottom. And you can see there's a difference using the four-strata method in that intermediate-low and intermediate-high group. The high is clearly high, high is clearly high risk, but there's a difference in that intermediate risk group. And so we're talking about how that group has too many people and does it really discriminate, and now we have a way of dividing that intermediate risk group into two groups that are clearly different in terms of their risk and in terms of their survival.

And it also is more sensitive to change. I showed you in the Italian literature how there's not that much movement and we are going to see using the four-strata method that there's more movement. So here are these curves that are a little confusing but what we have on the left is where a patient starts, low, intermediate, again, about 70% of the patients are intermediate or high risk. And you can see on the right where they are at first assessment, low, intermediate, high. They went on to death or lung transplantation or there was no risk assessment available. And in the three-strata method, you can see there was an increase in the proportion of the patients from low risk at baseline at 16% to 28%. You can also see that about 10% of patients went on to death or transplantation. And only about 29% of the patients had a change in their risk category, either improving or getting worse between the two time points. And you can see also, it is very important, it was also demonstrated in the Italian literature, very few high-risk patients improved to low-risk status.

Now, if you take that French registry and you use the four-strata method, I think it's really quite impressive here. So at baseline, you see that we now have four groups and you can see there are really clear cut points in those intermediate risk patients. About 33% fall into

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the intermediate-low risk and about 40% fall into the intermediate-high risk. And so these are all the same patients. Again, 10% had early death or transplant and 18% had no data available. And you can see, similarly, there's an improvement in the number of patients who are at low risk. Still not where we'd like. Look at this, still only 24% of the patients at low risk, but there was a higher proportion of patients who changed their risk strata. It's more sensitive to change. 39% rather than 29%. And you can see, again, 10% of the patients worsened by at least one, but 32% improved by at least one category. And you can see there were even more changes here in the intermediate-low and intermediate-high risk. You can see this really helped us assess patients better in terms of the response to therapy.

Moving to more tiers, will this refine treatment approaches? I can tell you in my practice it already has. The four-strata risk methods are based on these refined cutoffs for functional class, but in particular, six-minute hall walk and biomarkers and they're more sensitive to prognostically relevant changes in risk with therapy compared to the three-strata model and I think they're very useful in clinical practice. Again, in all of these databases, very few patients are at low risk at the time of diagnosis and in the COMPERA registry, at the time of diagnosis, the low risk and intermediate risk survivals were about the same, but that changes with therapy. I really want to stress that response predicts response. No matter where people are at the time of diagnosis, if we can get them to low risk, we're going to do much better with them in terms of their long term outcomes. The four-strata model demonstrated changes in risk from baseline to the first follow-up in about half of the patients compared to less than a third in the three-strata model. And these changes in risk from baseline to first follow-up, including in those two different levels of intermediate risk, were associated with important changes in long-term mortality risk.

So let's talk about assessing risk. What needs to be done at every PH visit? And I think this is really easy. It's very, very straightforward.

I love this particular graph that really highlights the importance of a multiparametric risk assessment, and we do this in clinic. So the clinical assessment, you talk to a patient, you assess their functional class, you assess how rapidly they've been progressing, you ask about syncope, you examine them, you look for signs of right heart failure. That's all very, very important as we manage our PH patients. Exercise tests are important, and we do a six-minute hall walk in just about every patient at just about every clinic visit. Some centers use more sophisticated exercise testing, such as cardiopulmonary exercise testing. We measure biochemical markers. We draw their blood at every clinic visit. We're checking for volume status or CBC, lights. We're assessing some of the potential side effects of therapies like LFTs. So we do a BNP or NT-proBNP with their blood draw at every clinic visit. And then we do imaging. We don't necessarily do an echo every visit, but we do it relatively frequently, and we look at some of the signs listed there, right atrial area and pericardial effusion. Those are the things in big databases that have been associated with prognosis, but in reality, I think this is one of the limitations of our current system. We don't have an imaging assessment of RV function, and when I go look at my own echoes, I'm looking at that RV function, and that is something that I think is very important in terms of managing a patient. And then of course, we don't do chemodynamics at every clinic visit, but occasionally we repeat chemodynamics, and we look at those very important markers of RV function on hemodynamics, including right atrial pressure, cardiac index, and mixed venous saturation.

So those are the multi-parameter variables. And while we may have many different risk assessment tools, many of them look at the same important variables. REVEAL 2.0 has 14 variables that include both modifiable and non-modifiable variables. We've talked a little bit about the variables included in the French Pulmonary Hypertension Registry and in the COMPERA registry. And here's a list of the ones that overlap in all these registries and are very important in predicting prognosis: functional class, hall walk, biomarkers, cardiac index, right atrial pressure, and SvO2, which tracks very closely with cardiac index. So those are all important markers. Again, those first three, we do it every single clinic visit and the predictive consistency of these variables makes them indispensable in the accurate prediction, no matter which treatment or which risk score, which algorithm you use.

So here's a little comparison of some of the algorithms. Again, REVEAL is more complex, and some of them have as few as three and as many as six variables, and most of these registries were very big. Most of them included different types of pulmonary hypertension. Although the French Registry really was limited to idiopathic anorexigen and, or I should say drug and toxin and heritable PAH. They've all defined low risk in different ways, but they're all very consistent. If you are at low risk, your one-year mortality is very, very low.

Now, as we talk about scoring and the like, we should really focus on some patients in whom screening is appropriate as well. And this was a topic of conversation at the 6th World Symposium. It was also a topic of conversation in the ERS/ESC Guidelines. There are certain patients, certain diseases or diagnoses that predispose to pulmonary hypertension. PH due to interstitial lung disease is something that we look for quite aggressively now, particularly given the availability of treatment for those patients. The most common cause of pulmonary hypertension in general is left ventricular systolic or diastolic dysfunction. Of course, patients with connective tissue diseases should be screened. And of course, patients who've had acute PEs may go on to develop chronic thromboembolic pulmonary hypertension. I think the most clear cut group to think about screening are those patients with the connective tissue diseases, given the high prevalence of PAH in the scleroderma population. There's some different methods for screening. At Michigan, we use the detect equation, but there are also options for looking at echo, DL, biomarkers and the like, but it's important to screen those patients. These

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are the patients that I see that have the least advanced disease, and it's really very rewarding and great for the patients.

So, effective PH care, do we need to rethink best practices for patient follow-up? I really need to emphasize that the goal of treatment of PAH is getting to patients at low risk, to getting the patients in the green zone, and as many of the variables in the green zone as we can get. And we have many tools to do that now, as well.

Combination therapy has been shown to be effective in treating PAH, and as part of all of the treatment guidelines. Currently, commercially, we have three pathways that we target, the nitric oxide cyclic GMP pathway, the endothelin pathway, and the prostacyclin pathway, and we have over a dozen FDA-approved therapies that are either oral, inhaled, or parenteral. And it's important to consider how combination therapy can be used to optimize care in clinical practice.

Now, the initial therapeutic approach is important, because most patients I think should start on combination therapy. In some patients, a very small proportion of patients, primarily those with idiopathic, heritable, and anorexic or drug and toxin-induced pulmonary arterial hypertension may respond to calcium channel blockers, and we identify those patients based on how robustly they respond to an acute vasodilator, such as inhaled nitric oxide at the time of their initial right heart catheterization. And of course, if they respond, drop the mean pulmonary pressure by at least 10 in the setting of a normal cardiac output. Those patients might be appropriate to treat with calcium channel blockers, but that's step one. Step two is you need to follow them clinically, and see if they improve to functional class one or two with just the calcium channel blockers, without the need for additional therapy. Those patients, very privileged patients may have a great long-term outcome with a simple, inexpensive, well tolerated therapy. But of course, those patients are very few and far between. The majority of patients will be non-responders to acute vasoreactivity testing. And those who are in the low or intermediate risk group, we generally treat with oral combination therapy, with an ERA and a PDE5, and there's a vast amount of data about how effective that combination therapy is as initial treatment for PAH. Some patients with PAH were not included in those clinical trials, for example, those with portal pulmonary hypertension, or those with many risk factors for diastolic dysfunction. And sometimes we go a little more gingerly in those patients, we start with monotherapy, and we reassess them a little more carefully before starting a second therapy. Of course, those patients who are treatment-naive, and fall into the high-risk category, we generally use initial combination therapy that includes a parenteral prostacyclin.

Let's say you do that, and the initial therapy does not get the patient to low-risk status, then we need to do something different. Remember, I said that the last part of the algorithm the reassessment part is actually the most important part of the algorithm. It's doing a structured follow-up and assessing risk after the first treatment choice that you made. And if the initial treatment approach results in something other than low-risk status, we need to do something more. If they're still at intermediate risk, we need to escalate, perhaps to triple combination therapy. If they're still at high risk, or they've progressed to high-risk, then we for sure need to do something more, and that probably includes a parenteral prostacyclin therapy. If you're successful, if that second treatment step gets you to the low-risk status, that's great, but then, remember, you need to continue the structured follow-up. The goal is to attain and maintain low-risk status, which requires continued structured follow-up. If after the second step the patient is not at low risk, if they're still at intermediate or high, then one needs to escalate to maximal medical therapy that includes a parenteral prostacyclin. And patients on follow-up with a low-risk status who deteriorate, this is why structured follow-up is so important, cause sometimes the disease can progress. If they deteriorate to intermediate or high-risk, they should be treated with more aggressive therapy. You need to escalate to double or triple or maximal combination therapy.

So, if we are rethinking the risk tiers in PAH, do we also need to rethink the management strategy? I'd really like to emphasize, we're doing better with our risk assessment, now we're refining that intermediate-risk group. It's not just green, yellow, and red anymore, we need to think about the shades from light yellow, through orange to deep orange in that intermediate-risk group. Because I do think that group is very, very heterogeneous and it does influence our treatment decision. Those patients at the higher end of intermediate-risk may act more like high-risk patients, they may have a poor prognosis, they may benefit from more aggressive therapy. So as we think about our intermediate risk patients, we have a variety of treatment options for them. Those patients more to the left of intermediate may be appropriate for dual oral therapy, but those patients who are more orange might be more appropriate for combination therapy, triple combination therapy that includes a parental prostacyclin up front. So we really need to try to explain this to our patients and really have a conversation of risks and benefits and shared decision making. We know that there are risks and uncertainties about the potential benefits for maximal medical therapy, including parental prostacyclin in some of those more intermediate risk patients. But I would argue that that recent French data helps us. I think it was pretty impressive looking at the benefit of upfront triple therapy with the parental prostacyclin in that intermediate risk group. So to me, I feel like that's a really wide group and I think about them very differently now and I think the four strata approach helps them. I think no matter what you decide to do with that baseline time. And I know I've been there. So many of my patients who I'll call orange patients or intermediate high-risk patients, despite me talking very passionately about the improvement in prognosis with combination therapy that includes a parenteral prostanoid that they look at me and they say, hey, anything, but the pump, let me try something, but the pump. And I think that's okay as long as you watch them closely. And we are very

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aggressive now about reassessing those patients within three months and then talking again about the parenteral prostanoid if they're still in the intermediate risk, or especially if they're on the more orange side of intermediate risk.

Initiation of triple sequential oral combination therapy may be appropriate for some patients who are not in the high risk. And I think it's really important to remember that that even though I'm touting our risk assessment, we've learned a lot about it. It's not perfect, and the person who keeps me up at night is that younger person, you know, that 18 or 20-year-old who otherwise is in really good shape and they walk over 440 meters, it may be that they're predicted as 700 and they walk 450. So they score well on the risk assessment tools, but they're still not where they should be. So they may have pretty good symptoms because they're otherwise in good shape, but they're sick, they have a high PVR, they have RV dysfunction. Those patients worry me. So sometimes we get a little bit more aggressive in those patients and go to triple therapy may not be parental process cycline, but maybe an oral prostacyclin, even though they're still functional class two. While there are other patients who may have other phenotypical characteristics that convey a poor prognosis and things like a connective tissue disease who may benefit from sequential combination therapy. And of course, the IV prostanoid should be included in combination therapy for high, and some of the intermediate-risk patients at the time of diagnosis.

So, summing it all up. Are we at the threshold of a change in how we approach risk and treatment in PAH? Well, we've learned a lot. There've been so many great publications over the past year or two. EAH risk-assessment algorithms are gaining acceptance as a means to objectively measure a patient's progress in therapy towards the goal of attaining and maintaining a low-risk status. To date, most treatment assessment protocols divide the population into three groups, low. intermediate, and high risk. However, about 70% of patients fall into that intermediate-risk zone. And some of these patients are sick. They may be higher, closer to the high-risk zone than that general categorization of intermediate-risk suggests. Recent re-analysis of risk-scoring algorithms for PAH from the French Pulmonary Hypertension Network and from COMPERA have now helped us subdivide that large group of intermediate-risk patients into two different strata, such that we have a total of four strata. Low, intermediate-low, intermediate-high, and high risk.

Patients with intermediate-high risk status are likely to require more aggressive treatment measures, including prostacyclins, and even triple therapy. Risk scoring for PAH is not only prognostic, but it helps us drive the management strategies. And I think this has been particularly helpful with that intermediate-risk group dividing them into intermediate-low and intermediate-high. And even for PAH patients with advanced disease, risk scoring suggests better alternative practices create more realistic options for lung transplantation. Thank you.

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