Pros and Cons of the 2022 ERS/ESC Guidelines: Practicality vs Real World View

This spring, Dr Thenappan Thenappan, University of Minnesota, Minneapolis; Dr Marc Humbert, Université Paris-Saclay, Paris; Dr Vallerie McLaughlin, University of Michigan, Ann Arbor; Dr Hilary DuBrock, Mayo Clinic, Rochester; and Dr Charles D. Burger, Mayo Clinic, Jacksonville, Florida, gathered to discuss the 2022 ERS/ESC guidelines.

Dr Thenappan Thenappan: Welcome to our roundtable discussion, pros and cons of the 2022 ERS/ESC guidelines, practicality versus real world view. As you know, the ESC and ERS published new guidelines for the diagnosis and management of pulmonary hypertension in August of 2022, with an intent to improve care for patients with pulmonary hypertension. First, I want to congratulate our European colleagues on this monumental task.

The new guidelines have made several important changes, including a revised definition of precapillary pulmonary hypertension with the lower PVR threshold of 2 Wood units, has provided pathways and guidance for early diagnosis of pulmonary hypertension, a different risk stratification approach for patients with PAH at the time of diagnosis and during follow up, a modified treatment algorithm for patients with PAH with a focus on comorbidities, which I think is very important, multimodality treatment approach for CTEPH, and finally, and not least, is the recognition of severe forms of PH associated with left heart disease and chronic lung disease to better understand them and develop novel therapies.

Undoubtedly, these new guidelines have shed light on many areas in the diagnosis and management of pulmonary hypertension. However, it has also created potential disagreements in some areas. Thus, to discuss the pros and cons of these new guidelines, we have assembled an amazing group of panelists and friends here today. These are world-renowned experts in the field of pulmonary hypertension, and we are really delighted to have them. We have Dr Vallerie McLaughlin, who is a Kim Eagle endowed professor of cardiovascular medicine and director of the pulmonary hypertension program at University of Michigan in Ann Arbor. We have Dr Marc Humbert, who's a professor of respiratory medicine at the South Paris University in Paris. He's also the director of the French National Reference Center for Pulmonary Hypertension and more importantly, he was one of the members of the guidelines writing committee. We have Dr Charles Burger, who is a professor of pulmonary and critical care medicine at the Mayo Clinic in Jacksonville, Florida. Dr Burger was our past editor-in-chief for *Advances in Pulmonary Hypertension* journal. Finally, but not least, we have Dr Hilary DuBrock, a rising star and associate professor of pulmonary medicine at Mayo Clinic in Rochester.

With that, I'll start our discussion with the first question. Probably I'll start with Dr Marc Humbert. Realizing you have a potential conflict of interest since you are on the committee, what is your overall impression of the new guidelines?

Dr Marc Humbert: Well, thank you very much for the kind invitation. I am really happy to be with you today. I would like to add just one thing on top of your introduction, which was excellent. There is a very important thing in the guidelines. We included patients in the guideline taskforce, and they are authors of the guidelines. I think that's something really important for the discussion today. That being said, producing guidelines, it's an exercise, which is very strict. When you use the word disagreements, I would contest that a little bit.

I mean, the facts are the facts, but they are either very strong evidence, and we write the evidence and the higher rating is 1A.

They are less robust evidence and you can go down to 2BC and even less sometimes when we are less sure of something we consider as important for future development. I would like to say that the guidelines are interesting, of course, and that it's a real challenge to produce those guidelines with a diverse group of people. Finally, is the way we develop it is systematic review, systematic analysis, and usually we end up with good quality data we can rate in terms of evidence, so I would pose here.

Dr Thenappan: Anybody else? Dr McLaughlin, your thoughts on the guidelines?

Dr Vallerie McLaughlin: First of all, I want to congratulate Marc and the whole committee. They did such a wonderful job on this document, this very thorough, very thoughtful document, so kudos to you. I would also say that there are always going to be areas that are open to interpretation of how you translate evidence into clinical practice and areas that might even have new evidence since the guideline decisions were made. I mean, it takes a very long time to create those guidelines, so I feel like there might be some areas where further discussion might lead to a better next set of guidelines when they're available. I think we all need to collaboratively discuss those areas to progress our field forward.

Dr Thenappan: Dr Dubrock or Dr Burger, your thoughts on the guidelines?

Dr Charles Burger: Yes, thank you. I couldn't agree more with Vallerie in congratulations to Dr Humbert and his colleagues on the guidelines. I real-

ly have enjoyed delving into them. It definitely represents a lot of work. How you pulled it off, I don't know. I think it would be almost impossible for us to support a similar endeavor in the US. There is some tension that is generated at times by these guidelines in the US. For example, it's difficult, I think, for all the patients to get to the centers despite our recommendation to do so. The diagnosis and the delivery of care for pulmonary hypertension is quite a diverse practice across the 330 million in the US in the 50 different states.

Practice has evolved, in my experience, with general clinicians, who don't have subject matter expertise in every rare disease that they see, relying on a quick review of the guidelines on their phone and almost mindlessly following them in a rote way. That, of course, may not necessarily involve careful consideration of the individual patient's circumstances, what's the difference between a diagnostic threshold and a treatment threshold.

There can also be some controversy that's created just in the translation of guidelines to clinical practice. Not really around the rating of evidence as it would currently exist, and certainly not around the effort to try to provide earlier detection in the subgroups that you emphasized in the document, connective tissue disease and CTEPH, for which there's lots of interest, but rather understanding whether or not the efficacy of these medications that are approved when the threshold is 25 or higher for the mean PA pressure, might also translate into earlier diagnostic thresholds for that pressure.

Then, of course, now around an even earlier threshold with the pulmonary vascular resistance. While some tension exists in the application of guidelines to practice due to the differences in the practices in the US versus Europe, I enjoy the controversy around that, quite frankly, because I think it then generates interest, further conversation, and as Vallerie said, maybe some opportunities for refinement going forward. Again, congratulations.

Dr Hilary DuBrock: I'd like to echo the comment that it's really important that patients were included in these guidelines, and I think it's a good standard to set moving forward of incorporating patients and patient-reported outcomes in both guideline development and clinical decision making. Also, I liked how this set of guidelines acknowledged that pulmonary hypertension is really heterogeneous. Many of the patients that we see in clinical practice don't necessarily fit our textbook definitions and were underrepresented in clinical trials, and thus require a more individualized approach to treatment.

I think that this individualized approach to patients was an important emphasis in these guidelines and also validated what we see in clinical practice where patients don't always fit neatly into one category. Certainly, I am also hopeful that these new definitions will lead to meaningful improvements in diagnostic delays, which I think is one of the major things we still need to improve upon within our field.

Dr Thenappan: That's a very nice way to start our next conversation. Maybe we could start with the new definition. What do you think the strengths of the new definition of PVR less than 2 Wood units for the precapillary pulmonary hypertension and what are all the things we should be careful about?

Dr Humbert: If I may start, first, thank you very much for the very nice start. I think we did not want to make a revolution, but we just wanted to identify the upper limit of normal of mean PAP and pulmonary vascular resistance. We made a systematic review with Gabor Kovacs and the committee. What we did is setting the upper limit of normal and any value above it defines pulmonary hypertension, which is a hemodynamic state, not a disease.

Then it's our job together in PH centers, not in any place and that's something we need to discuss maybe later. Defining the 2upper limit of normal establishes a limit above which you can have a wide landscape of different conditions ranging from group 1 PAH, group 4 CTEPH, and the very, very common group 2 and group 3 PH. Then, Charlie said something very important about it's not an indication to treat immediately, of course. It's just the start of the process.

Dr McLaughlin: Marc, I would be very curious to have a little glimpse of what the committee discussed when talking about the hemodynamics with respect to wedge pressure because we lowered the mean PA pressure at the last world symposium and now you also lowered the PVR and you're talking about really the upper limits of normal when really 15 isn't a normal wedge. In my view, there's a little inconsistency there. Tell me what the conversation was around leaving the wedge cut off at 15 versus moving it to 12.

Dr Humbert: Honestly, I think we kept it for the next round of revision because the consequences of lowering capillary wedge pressure are quite important in terms of excluding a group of patients who currently are treated with approved drugs and who might become more challenged if we lower the mean pulmonary capillary wedge pressure from 15 to 12, but you know me. I was really in favor of considering the wedge pressure as early as 2022 guidelines. We decided that first there will be a world symposium next year and this world symposium should really take care of the unmet portions of the guidelines and the capillary wedge pressure is very important to reconsider.

We should be cautious because if we lower the mean wedge pressure to 12, there will be a large group, I would say, of patients who may be in difficulty.

Dr McLaughlin: You're right. It's a very delicate area. All these patients are different and so I get that the 55-year-old with heritable PAH, who has a mean PA pressure of 50, if she has a wedge of 13, she's still PAH. With lowering it to 12, there may be some patients with other comorbidities who have a mean PA pressure of 24, and a wedge pressure of 15, and a PVR of 2.1 and that's a little bit of a different patient. I think it's a very complex issue.

Dr Humbert: I fully agree with that. Clearly, later in our discussion, you will see that we are very, very cautious when we discuss treatment of people with

cardiopulmonary comorbidities and that many people are difficult to categorize, and that's a very important point. That's the reason why what we said in the introduction is so important, being treated in expert center or at least PH centers with multidisciplinary teams and a lot of discussion around each case.

Dr Burger: I think it also creates a dynamic around using these thresholds in a very strict sense, as you articulated, Val, for purposes of research and discovery and better understanding high-risk groups, as opposed to clinical practice. There's always that challenge for strict recommendations based on evidence to identify those phenotypes of special high interest, certainly following clinically, and perhaps intervening earlier than we otherwise would, if there is drug approved for that hemodynamic definition. That is in contrast to having a standard recommendation for everyday clinical practice that's juxtaposed to a guideline that's very comprehensive in its science-based, research-based, evidence-based approach.

Dr Thenappan: The one advantage of lowering the PVR in my mind is identifying the other groups like left heart disease and lung disease. We could probably identify these patients early and aggressively treat their left heart disease and lung disease, which I think would be very important in this patient population.

Dr DuBrock: One challenge I have with the lower PVR threshold is how do you discuss it with patients who have a diagnosis of pulmonary hypertension by the new criteria but don't necessarily qualify for PAH therapy? This happened to me just last week. The patient I saw had a mean PA pressure of 23 with a PVR of 2.2 Wood units. I find it difficult to tell them that they have pulmonary hypertension but to not have any therapeutic options. It's a challenging situation and I'm curious how other people approach and discuss this scenario with patients.

Dr Humbert: I can start briefly. The patient should be characterized more completely in terms of phenotype. An elderly multimorbid patient is not the same than a BMPR2 mutation carriers. As you know, we follow very aggressively BMPR2 mutation carriers before having any symptom. Somebody would carry a BMPR2 mutation with that presentation would be followed very carefully every 6 months and would certainly be treated as early as possible if we can, but we can't treat these people at this stage. Sometimes okay, but at this stage, no. An elderly lady or gentleman with multiple morbidities, I think I would be quite reassuring.

I would say what Thenappan said. These patients have to be optimized in terms of cardiopulmonary comorbidities and followed up by cardiologists and pulmonologists. Every single patient is a story.

Dr Burger: Yes. I would agree with that. That's the stance I've taken. I don't know if it" absolutely the right stance but that we do want to pick this up earlier. We don't know that our therapies have efficacy because it hasn't been studied in a thorough way to know that. Nonetheless, increased attention to monitoring those patients. Close monitoring seems advisable in those groups in whom we think that this is likely to progress. Usually that helps but doesn't mitigate their anxiety. Certainly. I think you have to take extra steps to do that in some cases, but it does present a bit of a challenge, like you said, Hilary, that we're not necessarily used to.

Dr Thenappan: All of us would like to have a clinical trial that shows the safety and efficacy of pulmonary vasodilator therapies in PAH patients with a PVR of 2 to 3 WU. However, I would argue that it will be hard to find these patients. As you all know, still patients present to us at a later stage of the disease with PVR ~ 10 WU. I am worried that we are not going to have enough patients, and it will be difficult to find endpoints as these patients are not very sick. Do we think it's realistic to plan a trial for patients with PVR 2 to 3 WU only?

Dr McLaughlin: I don't think so for the exact reasons you said. For specifically a trial in patients with a PVR of 2 to 3, they're few and far between, and what do you use for the endpoint? They're probably functioning pretty well. I do think that it's quite possible that future trials will change their hemodynamic entry criteria to a PVR of greater than 2 and very likely there'll be so few patients with a PVR between 2 to 3 in those trials but probably drugs will get labeled for that if the entry criteria change.

Dr Thenappan: Thank you.

Dr Humbert: Yes. Maybe you can enrich the information with registry data. There are many good quality registries worldwide and I always insist that the entry criteria in the registry should be enlarged in order to have populations monitored with these very early levels.

Dr Thenappan: That's a great point. I wanted to bring the next topic. The guidelines have recommended risk-stratifying these patients differently at baseline and then at follow-up. At baseline, patients are categorized into low risk, intermediate risk, and high risk categories, but at follow-up, patients are stratified into low risk, low-intermediate risk, high-intermediate risk, and high risk for escalation of therapy. Curious to know your thoughts on this and how we should apply them in practice?

Dr Humbert: Once again, I may start and then the people can debate. We have been pragmatic. Why don't we need for strata baseline? It's because the initial treatment decision is rather simple. It's either 1, 2, or 3 drugs and for people without comorbidities, we strongly advocate for initial oral double combination therapy, or initial triple combination therapy, depending on the presence or absence of high risk. That's pragmatic for the initial presentation, and we advocate for quite aggressive treatment for these people. Then at follow-up, it's more delicate. Having 70% of the patients in the intermediate risk category with traditional risk stratification approaches was not acceptable.

We decided to try to separate those intermediate with the lowest risk of pro-

gression and mortality versus the ones with the highest risk of mortality in order to offer the people with intermediate-high risk a more aggressive approach in terms of treatments. Of course, at baseline, and I know that Vallerie is going to advocate for that and we do it sometimes in France, at baseline, you have some intermediate risk who have a lot of, let's say, borderline high-risk characteristics, and these people may be considered with a more aggressive approach, but I let Vallerie comment.

Dr McLaughlin: Marc knows me so well and I would say that I would gently challenge what he said that it's simple at baseline. It's actually French literature that showed a benefit in some of these intermediate patients who get upfront triple therapy that includes a parenteral prostanoid. I am a strong advocate of perhaps looking a little bit more closely at that intermediate risk group at baseline, and while it does not appear this way in the figure, it's certainly commented upon in the text in the ERS/ESC guidelines that some intermediate risk patients who have high-risk hemodynamics might be considered for more aggressive therapy that includes a parenteral prostacyclin.

It's in there. It's just not in the figure. We do not disagree so much, Marc, but I do gracefully challenge that.

I do think the 4 strata at follow-up is really, really critical. I think both the COMPERA registry and the French registry did a nice job of putting those papers out right before the guidelines and was able to be incorporated there, which I think is very important. I do also want to comment that our risk stratification tools are imperfect and there are other things that should be considered as well. I will have to tell you that my very favorite figure from the guidelines is Figure 4, where it goes into all of the echo images that are so critical to assess the RV. Marc, I tell you, I want to laminate that figure and hang it in every single echo lab in the world because we just don't do that as well. I just would put in a plug for thinking about RV function as a complement to the objective risk assessment tools that we have.

Dr Thenappan: Anybody else?

Dr Burger: Yes. I would agree that incorporation of the echo and the explanations that accompany it, cardiac imaging if it's available, additional ways to distinguish those folks on the high end of that intermediate risk in whom you might want to consider more aggressive therapy at the offset, is very important. It's hard to do because some of these values may be disparate, what you might see on echo versus the hemodynamics versus cardiac MR at times, but when they're consistently bad, I would push for aggressive therapy including an infusion prostanoid upfront.

I really like the 4 stratas. Very simple, very point-based, easy. My only concern is that as advanced therapies hopefully continue to be improved and we're on 3, 4, maybe more, what exactly is low risk? Is up to a 5% mortality at 1 year really low-risk, and are there additional ways to be discriminatory in that group? Maybe REVEAL Lite gives you a little extra discrimination just because each point value has a linear Kaplan-Meier curve that's a little bit different from the one less than that and the one higher than that. I don't know that. It's just speculative, but I think is where if sotatercept gets approved or rodatristat or seralutinib and we're adding that on sequentially for patients in that low risk strata. How do we further tease out lower risk going forward?

Dr Thenappan: I think that's the great thing about the new guidelines. So far, none of the risk stratifications really accounted for RV imaging. The new guidelines have to be congratulated. They have included echocardiographic surrogates of RV-PA coupling and also included extensive cardiac MRI parameters, which I think is important.

Dr Humbert: Yes. Excellent discussion. I must say that I did challenge a lot of my colleagues who do imaging of the heart, and thanks to that, they generated data because to make guidelines you need data. That's something very simple but sometimes people forget, [chuckles] and they don't publish their good quality data, which it may be a single center retrospective but if it's good it will not be 1A. It will be 2BC or 2BD.

We can generate information and Vallerie very kindly mentioned our work in France on 16 patients in 2014 which influenced the guidelines, not with the highest level of evidence, but with good quality information. Of course, guidelines are a work in progress, and there are always questions. When you spot a question, for example, a question about the 4 strata, adding more information, et cetera, we have to generate data. I mean, that's always the big thing. You have to identify the question and try to make a study or at least an analysis which will enrich the guidelines.

Dr Thenappan: Anybody else have any other thoughts on risk stratification?

Dr DuBrock: I like the 4 strata at follow-up since I find it very practical. The parameters are simple, modifiable test results that you generally have available when you're seeing patients. It's helpful to discriminate intermediate-low risk from intermediate-high risk since we all know these are very different patients with different treatment approaches. For my intermediate-low risk patient, I'm probably going to add an oral prostacyclin if they're on dual therapy or change their PDE5 inhibitor to riociguat versus for my intermediate-high risk patients, I'm certainly thinking now about adding parenteral prostacyclin therapy. Although we are always incorporating other information into our clinical decision-making, such as RV function or patient preferences. I think this is a simple but also very practical way to outline specific treatment recommendations.

Dr Burger: I was just going to say I think the other advantage, and Marc has always been very gracious about this, is just emphasizing doing that risk assessment regardless of the tool that you favor, which also emphasizes follow-up that should be regular and then impact treatment decisions. I think that's what everybody agrees on, I hope. Then what tools serve you and are most appropriate for your demographic. Obviously, the choice would be up to you to know

which tool is best as the subject matter expert in your center.

Dr Thenappan: One of the things that I have struggled with is the simplified, noninvasive, risk stratification tools. Expert centers just don't go by the risk stratification alone. They look at the patient as a whole. I'm just worried about how this will be handled outside of the expert centers. For discussion, let's take the noninvasive 3-variable risk stratification model based on 6-minute walk test, BNP, and functional class. When we use this in a relatively older patient with PAH, there are multiple reasons other than PAH that could lead to higher serum BNP levels. For example, atrial fibrillation, left heart failure, and renal dysfunction can make your BNP go up. Likewise, the 6-minute walk distance can be influenced by multiple other factors. Could that lead to overtreatment?

Dr McLaughlin: Thenappan, I think that's one of the reasons why incorporating the echo is so important as well because you have all those comorbidities and other circumstances and they may be high or intermediate-high risk, but if you do the echo and the RV function is normal, then that's always my rationale to say they're not low risk, but their symptoms are not from pulmonary vascular disease. It's more likely related to those comorbidities. Those two really go hand in hand for me.

Dr Burger: That's not an uncommon scenario quite frankly, and we heavily rely on echo as well. To have a high BNP and a suboptimal 6-minute walk, but a cold normal RV is very illustrative and does influence treatment decisions.

Dr DuBrock: I also felt the statement that "low risk is not always achievable, particularly in patients with comorbidities" is really helpful because our patients often have comorbidities and it's hard to achieve low risk in these patients where their functional class and exercise capacity may be driven by cardiac comorbidities. It's good to acknowledge that additional pulmonary hypertension therapy may not help in these scenarios where symptoms are multifactorial. I think that was a helpful comment to include.

Dr McLaughlin: It also works the other way too. Especially in the younger patients who may walk 450 meters, but their predicted is 700 and they can do what they want. Then sometimes they have these big blown out right ventricles. These are the people that keep me up at night because they seem low risk, but the right ventricle is living on the edge. That's why, as Marc said earlier, every patient is an individual. We have broad generalizations that help us, but there are many individualities that need to be considered.

Dr Humbert: Yes. Thanks to all of you for this very rich discussion. In fact, I think as always, when we generate a simple tool, it attracts a lot of attention and people think that the simple tool summarizes the guidelines while it's an addition. It's here to help the clinicians and the relationship with the patients, but if you look at Table 17 in the guidelines, we don't say you have to do only the 3 noninvasive follow-up parameters. Of course, walk distance, functional class, and blood tests, BNP or NT-proBNP have to be done at each visit and as Charlie says, we have to repeat the visit even if the patient is doing well. We have to see them regularly but of course, we also do echo.

In my center, we do quite a lot of [unintelligible 00:34:47] and it's valuable sometimes to refine in young patients with no comorbidities sometimes. They look quite nice with noninvasive tools, but they still have low cardiac index, like at baseline, as Vallerie said, and PROs. I mean, we have to learn to use more PROs. I work in Europe, and we have European reference networks, and we are going to advocate for systematic inclusion of PROs at each follow-up in the patients. For the moment, it is good to have, according to the guidelines, but we may push more, and we need to have good-quality PROs.

Dr Thenappan: We have several new therapies on the horizon for PAH. How might the treatment algorithm change if and when new targeted therapies are approved?

Dr Humbert: Always work in progress. Always work in progress. That's a beautiful image of our field to see that we generate so much new evidence. We should be happy, proud of that. My dream would be that these guidelines become history as soon as possible. We have new data, new information. Clearly with Val right now, we work quite a lot on an invitation to think outside the box and have a look to the future. Of course, guidelines cannot do that at all. Very soon, we will be able to maybe use our current thinking on a look to the future and try to incorporate in a revision of the guidelines. I will let my colleague speak. We want these guidelines to be history as soon as possible.

Dr McLaughlin: Thenappan, I think what we know is that there's one agent, [unintelligible 00:37:28], sotatercept that has a positive phase 2 trial, and more recently, positive phase 3 trial. In the phase 3 trial, that therapy was used in addition to standard of care. Certainly, at the very least, you think it will likely be incorporated on top of standard of care when sotatercept is commercially available.

As you also know, there are other clinical trials with sotatercept looking earlier in the disease state and later in the disease state. Hopefully, that will complement our evidence base and give us more information about how that agent might be used along the continuum of our patients with pulmonary hypertension.

Dr Burger: Yes. I would say you'll have to fall back on the cohort that was studied, the subgroups included versus excluded. What was their functional class? What was the range of hemodynamics, 6-minute walk? Then what were the breakpoints perhaps as it was layered on top of standard background therapy to help guide, I think, future recommendations around when would you recommend using a newly approved agent in your patient? It's not going to be perfect, but I think you would come back to the efficacy trials and try to stick as closely

as possible to the inclusion and exclusion criteria that were used.

Dr DuBrock: I think it's exciting to think about studying novel agents in different phases of the disease. For example, if antiproliferative agents can alter the disease process and vascular remodeling, maybe they are more beneficial earlier in the course of the disease? I think it's a really exciting area but agree that these therapies will be primarily approved for use in those types of patients that were included in the clinical trials, but certainly, I think a lot more is to come hopefully.

Dr Thenappan: The other question I want to bring to you all and get your thoughts on is the comorbidities. The new guidelines nicely differentiate this patient population rather than one-size-fits-all. It recommends monotherapy for PAH patients with cardiovascular comorbidities. At least in the US, the majority of the PAH patients we see have at least 1 cardiovascular comorbidity. How do we address this? If we follow the guidelines, the majority of the patients in our practice would be monotherapy to begin with. Is that what we should do?

Dr Burger: I would say I've heard Marc talk on this, so I've really appreciated his explanation. Despite that, I do struggle clinically with this because as I would approach a patient, if I'm convinced in my professional opinion that they have group 1 PAH, I'm really not paying too much attention to those comorbidities and would treat them with dual oral combination therapy. Now, on a practical note, with drug authorization and tolerance, this often plays out into sequential over a fairly short period of time, which was AMBITION in essence. It took 8 weeks to get a maximal dose of the ambrisentan and the tadalafil in that trial, so it's not too much different than the main trial that showed the efficacy. TRITON's design provided for more rapid upfront therapy in terms of the dosing. I think when I feel like they have it, I want to treat it aggressively, but that's just a practice bias. I can't give you data on that.

Dr Humbert: No, I appreciate that and I agree, in fact. When I see a patient with, to the best of my knowledge, a true group 1 PAH patient, I can of course start with initial combination therapy in those patients. In fact, the guidelines will have to be improved in that section because it can be misunderstood. It doesn't state that you should not. It says that you should be aware that there is an enrichment in patients with poor tolerability of initial combination therapy and with even some risks sometimes when you start with initial double oral combination therapy because of marked comorbidities mostly in elderly people.

At this level, I think that's where the personalized approach is so important and where sometimes a multidisciplinary approach is so important. If you look at the French registry, half of the patients are on monotherapy at first site. We are one of the most aggressive countries in terms of treatments, so it's interesting. In other countries, it's even more. I mean, we all know the registry data, so it means that it's maybe a mistake or maybe something people care about. They think it's better to start with 1 and then sequentially combine. We need to work on that.

We try to put together a randomized control trial in France on that very question, but it will take time and we need to find government funding because no company will fund that. We are currently discussing with the French Ministry of Health to have a support for that.

Dr McLaughlin: I think the issue is that the figure is really an oversimplification when we think about all these issues that we're talking about and individual patients. While both of what you said is correct, it doesn't come through in the figure. When you think about comorbidities, you also think about the duration and severity of those comorbidities, and you think about the severity of the pulmonary vascular disease.

Charlie, that 50-year-old patient with a PVR of 10, who just happens to have systemic hypertension that you're convinced is group 1 PAH, and you treat them along the left side of the algorithm. But it's the 75-year-old woman with hypertension, diabetes, obesity, and a PVR of 3.2 that is on the right side where we would all treat with just one thing, if at all. I think some of those details just aren't as apparent in the algorithm.

Dr Burger: In full transparency because I've been around a while, I have a ton of those patients that are on monotherapy that fit where you were trying to direct the thought process up front in the figure, so I get the nuances. You've explained it. They're on single drug therapy and they're doing fine, and I don't really know what their disease is, to be honest with you.

They seem to be doing well. The RV is remodeled to an extent. Their functional capacity is better. The other markers that we've used have improved and they tolerate the single drug, and I haven't been inclined to escalate therapy.

Dr DuBrock: Rather than defining these patients by the presence of 1 comorbidity, particularly in the United States where these comorbidities are common, I think it's important to consider the whole phenotype of the patient and whether they have multiple comorbidities. Age is also an important factor, and I think that's reflected in these example cases we're describing of varied treatment approaches. I think looking beyond just the presence or absence of 1 comorbidity such as obesity to determine if an individual has that left heart phenotype with multiple cardiac comorbidities is perhaps a better way to characterize the patients where our treatment approach might be different from someone who just has obesity with a BMI of 32.

Dr Thenappan: Moving on, do the new guidelines apply to non-European patients? Should they be adapted worldwide, or should they be modified? If not, what are all the considerations for diagnosis and management outside of the Western world? How should the guideline be adopted?

Dr Humbert: I can maybe start with my feeling. When we made the guide-

lines, the idea was global. We are now treating close in the borders of Europe. It's a global guideline. Of course, we know very well that there are countries where the drugs we propose are not available, not affordable. That's certainly the biggest challenge because I think US, Europe it can be a debate, but it's a rich-people discussion.

There are many countries and the vast majority of countries have no access to all the treatments we have. We want it to be global, and that's the reason why we are very, let's say, educational and that people should not focus only on the table and figures but read the text. When the text says you have to read the supplement, read the supplement, and read the reference. It's not a very simple guide, you open it on your mobile phone and you know how to treat them. That's important.

Then, of course, it's improvable and we need to improve it. What I love in our field is that we have the straight guidelines and we have the world symposium and other occasions to think outside the box and go a little bit quicker. The last thing I wanted to say was about the way we work in these guidelines. We are really strict in terms of evidence, and that's something we need to know. If we have a conviction, we are convinced that something is wrong, we have to do a study. I am myself trying to address some points, but it takes time.

Dr Burger: I would say that from my perspective, that more standardization around our approach to these patients as the basis for careful consideration and application to the individualized situation the better. It shouldn't be restricted to a certain part of the world, certainly. Having said that, there's wild disparities, as Marc just pointed out, in availability of drugs and clinical practice, and we just have to be mindful of that.

I think you go from the guidelines to a diagnosis and a recommendation for management in an individual. It's that translation and the expertise that's involved in order to make that translation is the most important aspect of it. We all hope that patients get to experts who have some experience and expertise to be able to make wise decisions. We know that isn't always the case, but that's a limitation that we face particularly in the US.

Dr Thenappan: Thank you, all. That's great. The next topic I would like to get your thoughts on is the individualized care for patients with PH due to left heart disease and lung disease with the PVR greater than 5 WU.

I will start with Dr Humbert, curious about why the PVR of 5 WU? How should we approach these patients? We know that there is no indication for pulmonary vasodilator therapy in these patients except for those with PH due to interstitial lung disease.

Dr Humbert: Yes. It was once again based on data which are not as strong as a randomized control trial but registry data. Because of the guidelines, we advocated for publication of registry data in group 2 and group 3 PH. Group 2 did not produce that many, but group 3 clearly identified both in COPD and interstitial lung disease that the PVR above 5 identifies a very high risk group.

Once again, you have to individualize the approach. If you have very advanced lung disease, it's not the same story than minimal shadows on both lungs. The devil is in the details, but it's a starting point. We don't advocate for treating mild PH in group 2 and group 3. We think you have to optimize the treatment of the comorbidity, but if you have significant elevation in PVR, you may consider, on a case-per-case approach, a treatment decision which has to be very careful and followed up very, very systematically.

My own approach is to do a randomized control trial, and that's something we try to do. In the US, you have approved drugs also for some patients with group 3 PH. You have to follow your own local possibilities.

Dr McLaughlin: Yes, I would agree. These are very challenging patients. I think it's always important to put in context the severity of their underlying disease. As Marc said, someone with horrible COPD and a PVR of 5, they may not benefit. They may actually get worse with some of these therapies. I think we have to have very long conversations with patients about the potential risks and potential benefits when we consider using these therapies on an off-label basis and watch them very closely.

Dr Burger: Yes. I think emphasizing the PVR particularly in the PHILD, that's born out in the increased data where PVR over 4 identified the group that had the best response and it was no great shakes at that, 21 meters in the treatment cohort at 16 weeks. It was the 10 meter deterioration in the placebo group that drove the statistical significance.

I don't know about COPD. I've been less impressed just on an individual basis. Obviously, the PERFECT trial was stopped with some safety concerns. I worry that in group 2 about obviously increasing upstream pulmonary flow when the cause of the PH is downstream in the left heart.

Even with a higher PVR, I do look carefully at the wedge and the v-wave with an acute vasodilator trial just to get some sense of what's happening acutely. The hemodynamic response does influence my decision, but that's just my experience.

Dr DuBrock: I think it's important to highlight these definitions and thresholds for PH from left heart disease. I don't typically treat them with pulmonary vasodilator therapy, but there are those combined precapillary, postcapillary pulmonary hypertension patients with a PVR greater than 5 who have disproportionate PH, and I think those patients really need further study. It's not uncommon that we're seeing those patients in clinic, and it's really hard to know what to do with them. Defining that PVR threshold, I think, is helpful just to guide further study of these patients.

My approach generally in PH ILD is to use inhaled treprostinil since it is an approved therapy in the United States and it is nice to have something to offer these patients without a lot of treatment options.

Dr Burger: I rely a great deal on chest imaging. If there is a great deal of

parenchymal scarring, then I think there is end-stage lung disease. We look at these patients and we know the lung is largely dead; therefore, it's a mechanical problem that requires a mechanical fix. If they're eligible for a transplant, you direct them that way. If they're not, it's difficult.

Dr Humbert: Yes. It's very important, Charlie, what you just said. We should never forget the transplantation in some of these patients because it's really a life-saving approach and for the most advanced patients, it should be considered.

Dr Thenappan: This is great. We are at the top of the hour. Maybe we can just end with closing remarks from everyone on the guidelines.

Dr Humbert: If you want, I start. Guidelines are really a work in progress, and at the end of the guidelines we have a section, Gaps in Evidence. That's really what you have to focus on. We need to have our field move forward. Maybe the next guidelines will be less comprehensive because we don't have to repeat the entire story. As a member of the European Respiratory Society, we more and more recommend to select a few questions and use a grade approach and we have a question, [unintelligible 00:56:46], what we call [unintelligible 00:56:47], and a grade approach.

It allows us to focus on the gaps in evidence, so maybe that's what we will do one day. Thank you for the invitation.

Dr McLaughlin: Marc, I just want to congratulate you and the whole team. It was really quite a tour de force, and we've learned so much from the guidelines. It's also raised some questions and some discussions and some opportunities to discuss at the world symposium and the next guidelines. That's actually good, right? If it was all cut and dry, it would be very boring. I think it's raised some important questions, but I just also want to emphasize, some of those figures are so beautiful, I want your artist, right? The echo figures, I love. The symptoms figures, I love. I think it's a really wonderful teaching tool.

Dr Burger: I would agree completely, Val. It's a wonderful starting point for conversations like the one we just had today, right? You can't begin to discuss what the definition should be or what the treatment indications are unless you have that starting point. It's a wonderful job by you and your committee, Marc. It's really been a pleasure participating today.

Dr DuBrock: I agree. It is a tour de force that was fascinating to read as it highlighted both the current evidence and also the gaps in evidence and areas for future research, which is inspirational in a way. I think this is an excellent framework that'll help guide us moving forward with advancing the field, which is really important. Congratulations and excellent work and thank you for the opportunity to discuss with everyone here today. It was an honor and was really informative and enlightening, so thanks.

Dr Thenappan: Thank you all again. It was a very enriching, thoughtful, and thorough discussion. I really appreciate everyone's time, knowledge and effort.