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Released: 11/30/2023
Valid until: 11/30/2024
Time needed to complete: 4h 49m

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

US Perspective on ESC/ERS Guidelines

Announcer:
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Dr. McLaughlin:
Thanks, Mike, that was such a wonderful overview. And as Mike said, that's a very comprehensive document. It's very evidence based, and the literature reviews are wonderful. And, you know, I honestly am friends and colleagues, with almost all the authors of the ESC/ERS guidelines, I think they did a wonderful job. But I do kind of have a few points that maybe I don't quite agree with, or maybe I think need to be adjusted a little bit for the U.S. perspective. And I'm going to highlight just a handful of those today. And mostly I'm going to talk about the hemodynamic definition, the diagnosis, the risk assessment, and the treatment algorithm.

And Mike has reviewed this data. So previously, actually, at the last World Symposium, the mean, pulmonary artery pressure was lowered from 25 to 20 based on some data. I don't know if anyone knows - does anyone know how the mean pulmonary artery pressure of 25 got established as being abnormal? Anyone know? Do you know?

Dr. Cascino:
I don’t.

Dr. McLaughlin:
Tom? Oh, have I told you this story before?

Dr. Cascino:
You have not.

Dr. McLaughlin:
Okay, how do you think it got established?

Dr. Cascino:
I think in the 80s, it was just made up.

Dr. McLaughlin:
Yes, essentially. So the NIH registry started in the 1980s. We learned so much from the NIH registry. And, you know, at that time, people were like, well, I don't know what a mean pulmonary artery pressure is, you know, that's normal. But, you know, surely 25 must be abnormal. Surely, 25 must be abnormal. And so, they established a mean pulmonary artery pressure of 25 as entry criteria into the NIH registry. And then ever since, a mean pulmonary pressure of 25 has been the definition. And as Mike so nicely alluded to, it's probably not really normal. So again, normal patients have, if you do big population cath studies, a mean pulmonary artery pressure of 14, a standard deviation of a little over 3 gets you a mean pulmonary artery pressure of 20 as being normal if you look at 2 standard deviations above the upper limits of normal. So that was done at the last World Symposium in 2018. But the change here is lowering the

pulmonary vascular resistance to 2 Wood units.

And I do take a little issue with this. And as Mike said, this is based on VA studies, retrospective VA studies showing that the mortality goes up once your pulmonary vascular resistance is over 2. Now, what do you think the most common cause of pulmonary hypertension in a VA population is? Yeah, exactly. Probably most common is Group 2 pulmonary hypertension, so they have some other left heart disease. And then probably the second most common is Group 3, COPD, you know, what have you. So how do you know they're dying because their pulmonary vascular resistance is over 2 versus their left heart or their lung disease is so bad that they have a higher mortality? So I personally think it's a little bit flawed to use this retrospective data in a very mixed cohort of pulmonary hypertension to redefine the pulmonary vascular resistance as greater than 2.

And if you think about how we treat our patients, a patient with a mean pulmonary vascular - or with a pulmonary vascular resistance of less than 3 has never gotten into any clinical trial, right? That's always the entry criteria, at least 3. Some clinical trials even have a pulmonary vascular resistance of over 5 to get into it. So now they're suddenly saying this is the definition. But for these patients with a PVR between 2 and 3, well, we don't know that you'd do anything for them because they've never been studied. And in reality, they're really hard to study. You know, we don't get patients with – Group 1 patients with PVRs between 2 and 3 all that often. If you look at clinical trials of PAH, most of the time their PVRs are 6, 7, 8, 9.

So you know, while I understand the academic exercise that they went to, I do find it a little bit flawed. So, you know, I think we have to kind of take this with a grain of salt and kind of see what happens to patients with a pulmonary vascular resistance between 2 and 3.

I also want to make one comment actually on the exercise definition, which now is back in the guidelines. So it's in, it's out, it's in, it's out, it's back in. I think there are a couple things to consider here. One is that when we do exercise in the cath lab to elicit pulmonary hypertension, I would say more than half of the time when the PA pressures go up, it's because the wedge pressure goes up. And really what we're eliciting is diastolic heart failure. And so we have to really think about that as we kind of give patients this diagnosis. And sometimes wedge pressures with exercise can be a challenge to measure. But I do think it makes more sense to look at the ratio of mean PA to cardiac output than just picking a number, you know, getting the mean PA over 35. Because again, you know, if your wedge goes up to 25 with exercise, of course, your mean PA pressure is going to go up.

This is their new treatment algorithm, which, you know, is a fine treatment algorithm. I think it's really more geared towards community physicians and starting to suspect pulmonary hypertension early and referring them to cardiologists or pulmonologists. You know, I do agree with like the fast-track if there's a lot of high-risk variables. I think this is less helpful at courses like this, you know, for people who are really interested in pulmonary hypertension, and really, to help them methodically go through the evaluation that they should do when they're seeing patients.

However, I think they did a wonderful job with their details on the role of echocardiography. I would like to make posters of this image and laminate them and put them in every single echo lab across the country. Because this really gets to the heart of something that we've been talking about for a long time. The echo is much more than what the estimated pulmonary artery pressure is. There are so many things to look at on the 2D and other aspects of Doppler, that tell us how much stress the right ventricle is under. And I think they did an absolutely wonderful job highlighting some of those parameters in this figure, as well as incorporating that into this little flow diagram. Because this now, nicely how says to you, you know, the first step is, what is your TR velocity? And you know, are we thinking, you know, likely PH or not likely PH? But then also do they have some of those other signs, right ventricular enlargement dysfunction, septal flattening, you know, all of those things. And even if the RVSP is not elevated, and we know RVSP, is not perfect, so even if the RVSP is not elevated, and they have signs of strain on their right heart, it puts them at an intermediate probability. And so sometimes you might say, I'm going to go through with the rest of the evaluation, I'm going to cath that patient, even though their RVSP is not high. So I think this is a really nice job that they did on the echo section, what to look for an echo, and then how to incorporate the data from echo into the decision-making as you go through the diagnostic algorithm.

They updated the risk assessment. And, you know, I think this table has evolved so much over the years. And I really think the community has done a wonderful job of looking at new factors and expanding factors for risk assessment. Many of these are well established, hall walk, peak VO2, biomarkers. And then there's some new ones here on echo the new one thing that they added is TAPSE/systolic PAP, as this has been demonstrated in a couple of studies now to have prognostic significance. They also added stroke volume index in MRI and cath. I would say that that intermediate-risk group, that's still a wide range, a 1-year mortality of 5 to 20%. It's a pretty wide range. And I think that's a wide range, whether you're intermediate at baseline or intermediate after your first assessment. And this has been a problem with our risk stratification for a long time. You know, we rarely get patients at the time of diagnosis in low risk, sometimes we get them in high risk, very high risk, and we know we need to be very aggressive with those patients including parenteral prostacyclins. But that intermediate-risk group is big, and that range is wide. And so, I do think we need a little bit more delineation of those patients.

And this is a study that was published from the French database, and it looked at basically how patients were treated, whether they were on monotherapy, dual therapy, or triple therapy with parenteral prostacyclins. And on the left, you see the high-risk patients. And obviously, the high-risk patients that were treated with triple therapy that included the parenteral prostacyclin did well. This observation has been made before. But this is the first time that someone has really demonstrated that in the intermediate group patients. So intermediate risk, a large number of patients, a large range. And in the French registry, the intermediate-risk patients who were treated with upfront combination therapy that included a parenteral prostanoid, did better, did significantly better than patients who are treated with mono or double therapy. So I'm not saying that every intermediate-risk patient needs upfront combination therapy with a parenteral agent. But I guess I'm using this point to say intermediate is a big group with a wide range of severity, and we need to really take a closer look at them.

And my partner, Tom Cascino, who you'll meet later today, and I wrote this editorial, this picture is really his brainchild, he's much more creative than I am. But I think we use color here to really demonstrate the problem with intermediate risk, it's not all yellow; there are some patients with intermediate risk, that have some high-risk features that are a lot more orange, they're a lot closer to red than they are in the yellow zone. And I think we need to take that into consideration.

And Mike mentioned the 4 strata calculation, which I really like it. It's very evidence base, and it takes that big intermediate-risk group and divides it into intermediate-low and intermediate-high. And those survival curves are really different. So they use this tool at follow-up. So here's the difference in the survival curves. So this is from the COMPERA registry. On the left, you see low, intermediate-low, intermediate-high, and high at baseline. And then at the time of the first assessment, you see the survival based on which of those 4 risk strata they fall into. And you can see that there is a difference between that intermediate-low and intermediate-high group. And while the intermediate-low was not as good as low, the intermediate-high group is not far from high, and I think really should be treated more aggressively. And that particular methodology was validated by the French. It's like essentially the exact same results in another database.

The ERS/ESC guidelines is really based on those methodologies, the 3 and 4 risk strata. Mike also mentioned REVEAL. You know, the point is you need to do some sort of objective risk assessment. And so, this is an option as well.

So, when we get to the treatment algorithm, I do have a couple of problems with this. So my first problem with it is why on earth they use 3 strata at baseline, based on what we just talked about, based on that wide range of the intermediate-risk group, based on that, you know, poor prognosis of the intermediate-high risk group, based on that French data that showed intermediate-risk patients treated with parenteral prostanoids did better. I am concerned about making it so simple at baseline as to low, intermediate, high.

Now, in all fairness, if you actually read the text, and nobody reads the 110-page, like maybe Mike and I read the 110 pages, but most people don't read it, they look at the pictures, right? If you actually read the text, in the text, it says there are some intermediate-risk patients who have some poor prognostic indicators such as a very low cardiac index that you might treat with parenteral prostanoids. So it says that in the text, but I don't think you get it from the figure. And I think that they certainly had the opportunity to acknowledge that intermediate risk is a wide range, and there are some patients in the intermediate risk group that should be treated more aggressively. They do go to the 4 strata method in the follow-up so, but I think that was a missed opportunity.

And then the other issue that I really am concerned about is the issue with saying patients with comorbidities should be treated essentially more gingerly, that you should start only one therapy on them. You know, I really hate that they use the AMBITION paper that I wrote as rationale for that, because that was, you know, a very small assessment of patients with multiple cardiovascular comorbidities that got entered in AMBITION prior to the amendment. So I don't think that should be used as rationale. The problem that I have with this is there's really no specificity around it. You know, what matters in comorbidities is the severity, the number, and the duration of comorbidities. And really putting that in context with the amount of pulmonary vascular disease. You know, so what do they mean here? Like, I get it, the 85-year-old woman with hypertension, diabetes, and obesity, who has a PVR of 3.2, yeah, that's a patient who may qualify as PAH based on a cath after she's been diuresed, but she’s probably not true PAH. And yeah, I would probably only give that patient a PDE5 inhibitor. I agree. But what about the 50-year-old woman with heritable PAH who just happens to have systemic hypertension, and her PVR is 10? You know, she has a comorbidity, but I'm going to treat her on the left side of the algorithm. So I do think that this figure is not exactly how we treat patients. And there's other things that need to be considered.

The second step using the 4 strata, I think is important. For the U.S., I would acknowledge also that we have inhaled therapies that are not really included in these guidelines.

So that's kind of just my editorial comments on the ERS/ESC guidelines.

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