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

Overview of Major Changes to ERS/ESC Guidelines for PH

Announcer:
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Dr. Cuttica:
Okay, let's get on to our session. So we're going to talk about the overview of the new ERS/ESC guideline recommendations. So, if you guys haven't seen this, this is the document that came out, published in 2022. It's a very long document, a little over 100 pages, but it sort of summarizes all you want to know, and probably more than maybe you ever want to know about current thinking about pulmonary hypertension. It's a nice document. There's a lot of nice information in there. So a good reference to have to go back and look through.

What we really want to highlight today in the next 15 minutes is we're going to review the background of pulmonary hypertension and pulmonary arterial hypertension. And then we're going to highlight the major updates that really came out in these guidelines.

So to start with, to kind of set the stage I guess for the day today, as we know, pulmonary hypertension, really just means high pressure in the lung. And when we think about pulmonary hypertension in general, right, this is the umbrella term that encompasses all different types of pulmonary hypertension. So PH, in general, just high pressure in the lung. And really the more important question then to ask when we think about the diagnosis of pulmonary hypertension is what type, or another way to think about it is where in the cardiopulmonary circuit in the connection between the heart and the lungs, where is the abnormality or the disease state that's driving that high pressure in the lung? Because it's this initial question that we think about that really drives the questions about management and prognosis in patients. So we can see in this schematic, the picture of the RV into the pulmonary artery, the pulmonary venous bed, and to the left side of the heart, and all the different areas where we could see it. And in the guidelines, the general classification scheme for pulmonary hypertension is generally stayed the same, right?

We think about this disease as being categorized into 5 major groups, that we think Group 1 or pulmonary arterial hypertension, we think of as primarily a vascular disease of the lung that affects the precapillary bed. Group 2 pulmonary hypertension is the type of pulmonary hypertension that is driven by left-sided heart disease, so pulmonary venous hypertension. Group 3 pulmonary hypertension is when we think about parenchymal lung disease, patients with underlying COPD, emphysema, either with or without hypoxia, but where the PH is really driven by destruction of the lung parenchyma. Group 4, as we'll highlight in the next setting, is chronic thromboembolic disease, diseases that are characterized by unresolved pulmonary embolism or chronic clotting in the lungs. And then Group 5 is the multifactorial mechanisms, the PH that can be driven by lots of different causes.

In the guidelines, there have been a couple of minor changes, or as of ours, the way we classify this. So there were changes as far as the way we classified reactivity and non-reactivity in patients with underlying primary pulmonary hypertension, and then some changes to the classification of Group 3 PH. But ultimately, the overall way we characterize and think about this disease stays the same. And each of these groups is really linked to underlying pathologic changes in the lung.

Probably the major change that came out of the ERC/ERS guidelines as we changed the definition, or the level at which we define pulmonary hypertension. So this is a disease that is defined by hemodynamics. Classically, we've defined pulmonary hypertension as a

mean pulmonary pressure greater than 25. This highlights the need for a right heart catheterization and making the diagnosis. But with the new guidelines, the threshold for calling someone as having pulmonary hypertension was lowered from 25 to 20 mmHg. We might say, well, this seems like a pretty minor change, why was this made? Or if you think of when you talk to people that were involved in the original definition of PH, 25 was somewhat of a random number that was chosen just to make sure we're capturing everyone. And now with years of epidemiologic data being collected in this, we know that the normal mean pulmonary pressure is 14 plus or minus 3. So the ESC/ERS guidelines decided to lower the threshold to 20, because 20 represents two standard deviations above what would be considered the population mean for pulmonary hypertension. So we'll talk when Val gets up for her talk, we'll talk about what this - some implications of the drop in the mean pulmonary pressure to 20 as part of the definition, but that's one of the major changes in the guidelines.

And we'll see here with this, we've changed also the threshold for pulmonary vascular resistance as part of the definition here. And again, this is based on epidemiologic data, mainly data out of the Veterans Hospital, big study that showed that a cut-off of a pulmonary vascular resistance of around 2 Wood units is associated with an increased mortality risk in again population-based study. So based on this information and the information around what the normal mean is with the standard deviation, these are the definitions of pulmonary hypertension now in the guidelines.

So PH is just a mean pulmonary pressure greater than 20. Precapillary pulmonary hypertension, or the Group 1 disease is a mean greater than 20, with a wedge less than 15 and a PVR greater than 2 Wood units. Isolated post-capillary pulmonary hypertension are those patients with left-sided heart disease where the mean is greater than 20, the wedge is elevated, the PVR is low, and then combined pre and post-capillary PH, we see the wedge elevated with an elevated PVR.

And then also new to the guidelines, or back in the guidelines now, is an attempt to define exercise-induced pulmonary hypertension. And we can see this is now being defined as a mean PAP to cardiac output slope between rest and exercise of greater than 3.

The other big thing that was highlighted in the ESC/ERS guidelines that I liked is they push towards earlier detection. So some algorithms trying to help people identify PH earlier and we can - this is one of the good things about the guidelines. If you look into this, there are nice flow diagrams for people to be able to go through this. I highlight here one of the recommendations so if you have a high suspicion for pulmonary arterial hypertension or CTEPH, the recommendation is to fast-track that referral to a PH center that can offer all available therapies for PH.

And then I want to highlight as well another thing that they talked about that I thought they did a really good job on in the ESC/ERS guidelines is the way we screened for PAH, really giving more information about how we can fully utilize echocardiogram as a screening tool for pulmonary hypertension. I think gone are the days where we should look at an echocardiogram and just say, oh, the pulmonary artery systolic pressure is elevated, this person has PH. We really want to use this tool to the best of our ability because ultimately, when we think about pulmonary hypertension of the right ventricle, we're really thinking about a disease that is being driven by increased right ventricular afterload. And that these chronically elevated right ventricular afterload can lead to these changes between RV and PA uncoupling. And then, the echocardiogram, really, this is a nice figure from the guidelines that show not just looking at the pressure estimate, but really looking at the structure and functional changes in the echocardiogram that we can look at to really guide us to say when should we be concerned about this disease? When or what else can we look at to tell us information about the right side of the heart, the complete hemodynamic picture of the patient?

And then finally, we'll talk about the PVR thresholds and implications for clinical practice thinking about close follow-up in these patients. How will this affect treatment? Making sure we're watching these patients with the lower threshold of pulmonary hypertension. And making sure we're looking and treating for risk factors associated with it.

So in summary for this, we're going to look at the mean PAP is greater than 20. And then PAH being defined as the mean greater than 20, a wedge – a PVR greater than 2.

And then the last thing I want to highlight in these guidelines is the recommendations they made around treatment algorithms for pulmonary hypertension. And really, there's a couple of things in here that were interesting. We're looking at the treatment of patients with Group 1 pulmonary arterial hypertension, one of the things that they split that led to a little bit of conversation or controversy around this that we'll talk about is stratifying patients between those who have a comorbid cardiovascular disease and those without cardiopulmonary comorbidities. We'll talk more about that in a second.

And these guidelines also highlight the need to use risk assessment in patients with PAH. This is one of the really exciting things has been in the world of pulmonary hypertension in the last couple of years, a lot of publications out of pulmonary hypertension registries, looking at all of the parameters that we followed in patients over the years that tell us about how they're doing and trying to put into an objective measurement, how we can classify the risk of a patient. And now they've codified this into the treatment guidelines and to use

these risk assessment tools to help us make decisions about treatment. So in this, we're highlighting using the first step after diagnosis, the 3 strata risk assessment where we're looking at low, intermediate, or high-risk patients based off of their parameters like the BNP test, the walk test, the echocardiographic findings. It doesn't really matter which risk assessment tool you use, whether it's REVEAL, REVEAL Lite, or ESC/ERS guidelines, but in this treatment algorithm, we want to use the 3 strata rule at the new diagnosis. And if you have a patient that is low or intermediate risk based on these risk assessment, you're going to use or think about upfront combination therapy as the recommendation here. And in high-risk patients, you're going to think about combination therapy with the addition of a prostacyclin, or prostacyclin analog.

And this is really based on data also from large clinical trials. So this is data from the AMBITION trial that looked at combination therapy versus monotherapy and showed improvement in patients that were treated with upfront combination therapy. I should have clicked and it would have told me the answer to that question. PDE5 plus an ERA, versus PDE5 or ERA alone. And then in the high-risk population, we're really thinking about triple combination therapy for maximizing their treatment.

And then again, a little bit of controversial area related to the guidelines is thinking about patients that have cardiopulmonary comorbidities, and the ESC/ERS guidelines making the recommendation to consider oral monotherapy for these patients. This is again based on a publication that Dr. McLaughlin put out that I'm sure she's going to talk about. But if we look at the AMBITION trial, and then looked at subgroups in that trial that had comorbid conditions. And looked at the long-term outcomes of these patients. So there seem to be in patients that comorbid conditions lower benefit with upfront combination therapy compared to the overall treat patient population in that trial. And there were increased rates of discontinuation.

But as we'll talk about in the next talk, if you look at this, right, there was a large benefit in the entire cohort receiving upfront combination therapy. And even in patients in this subgroup analysis with comorbid conditions, those patients still had a benefit with upfront combination therapy, it just wasn't as robust as the overall population.

And then the last couple slides here as we move into patients who have already been treated, and then their regular follow-up, these guidelines highlight using now a 4 strata risk assessment for follow-up. This now further delineates patients into low, intermediate-low risk, intermediate-high risk, or high risk to help make further treatment decisions. This is again based on WHO Functional Class, walk test, and BNP. And this is data showing that the 4 strata can further delineate sort of long-term outcomes in patients or survival. So we can use those to help us guide whether or not we make treatment decisions to escalate therapy.

So again, now the conclusions for this, we're going to talk about overall PH as a disease entity where we define this as a mean greater than 20. You see in this table, the definitions of pre- and post-capillary PH. We think about PAH as a progressive primary precapillary vasculopathy. Echo is a good screening tool. Right heart cath is diagnostic.

And then when we think about the treatment approach, we really want to think about instituting risk assessment in these patients to help us make treatment decisions. And then these treatment decisions around dual combination therapy for low- to intermediate-risk patients and triple therapy, consider triple therapy with the inclusion of a prostacyclin for those who are high risk, which again, it plays into the discussion of the diagnostic algorithm where we think about early referral of patients that we think are at high risk or that we're worried about, so that all treatment options are available on this patients.

So I'm going to stop there.

Announcer:
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