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Implications of Aggressive Therapy in 'PAH Without Comorbidities'

Announcer:
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Dr. Saggar:
Hi, I'm Rajan Saggar from the University of California, Los Angeles. And I'm going to talk about aggressive therapy in PAH without comorbidities. What does that actually mean?

Well, medical therapy for PAH where we are today, it's important to remember that the ultimate goal of medical therapy in PAH is to achieve and maintain low-risk status based on a multiparametric analysis, which I'll show you in a second. Over time, the recommended approach to medical therapy for PAH has generally evolved towards a more aggressive approach. However, despite the more aggressive initial upfront combination therapy approach that is advocated today, the available data from meta-analyses, from registry data, as well as retrospective data all suggests that survival has not changed significantly over time; thus, leaving a very high mortal disease in play. Less than half the patients receiving initial combination therapy actually achieve low-risk status. So with these problems in front of us, we still have a lot of work to do.

As we stand here today, the ERS/ESC guidelines in 2022 recommend the initial therapy for PAH without cardiopulmonary comorbidities should be based on a multiparametric risk assessment using the 3-strata risk classification system, shown here today. And you can see in this table, the different types of parameters that are used to make this assessment. And we risk stratify patients into low, intermediate, or high risk based on their 1-year mortality. Now the determinants here are on the left, and you can see that these are all clinical determinants of risk, and they're not assigned a point value as you will see in the 4-strata system in the next slide. All patients should receive upfront combination therapy, meaning two oral medications, specifically an endothelial receptor antagonist, and a phosphodiesterase 5 inhibitor. In addition, those patients deemed to be high risk based on this risk assessment, should receive upfront intravenous or subcutaneous prostacyclin. As you can imagine, using this 3-strata system, there is some room, some wiggle room, so to say, between the risk categories, both low, intermediate, and high-risk categories. So some of the aggressiveness of the approach can be determined by the clinician him or herself.

Now continuing with the theme of initial treatment in this population without comorbidities, why is upfront triple combination therapy not the universal standard of care in 2023? Well, for first evidence for that is the Triton study. This was a randomized controlled trial comparing dual oral combination therapy versus triple oral combination therapy. And it turns out that both arms had significant improvements in pulmonary vascular resistance on the order of 50%. And both arms improved the walk distance, the 6-minute walk distance by more than 50 meters, and there was no difference between dual and triple oral combination.

In addition, and importantly, the French experience with open-label upfront dual oral combination therapy using bosentan and sildenafil plus I.V. epoprostenol, actually showed that patients had a 3-year survival of almost 100%, and significant improvements in NT-proBNP and walk distance.

So, the story is not over in terms of triple upfront combination. And a lot of work is being done to look at this, but there is some

suggestion that triple upfront combination may be best served with non-oral therapy as the third agent but this remains to be seen.

Now in follow-up of patients with PAH without cardiopulmonary comorbidities should also be based on risk assessment. However, this is using a 4-strata risk classification. And you can see there's three variables. The functional class, the 6-minute walk distance, and the natriuretic peptide, whether it's a BNP or an NT-proBNP. In this system, you are given points. And you can see the points at the top there assigned to low risk, intermediate risk, intermediate-low risk that is, intermediate-high risk, and high risk. And what you do is you add up all of your points and you divide it by the number of variables and you round up to the closest integer.

Now here you can see that after you use the 4-trata system this is in follow-up of patients as opposed to initial therapy. And this determines how you add medical therapy. And you can see in low-risk patients, you continue medical therapy as is. In the intermediate-low risk, you either add a PRA, a prostanoid receptor antagonist, or you switch your phosphodiesterase-5 inhibitor to a guanylate cyclase stimulator. In the intermediate-high risk or high risk, you add an I.V. or subcutaneous prostacyclin, and you consider evaluation for lung transplantation.

Thank you very much for listening.

Announcer:
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