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https://reachmd.com/programs/cme/a-new-look-at-risk-assessment-models-changing-the-intermediate-risk-tier/14113/

Released: 05/31/2022
Valid until: 05/31/2023
Time needed to complete: 1h 04m

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A New Look at Risk-Assessment Models: Changing the Intermediate-Risk Tier

Dr. McLaughlin:
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 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

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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.

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