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Understanding Vutrisiran's Cardiac Effects in HELIOS-B

Announcer:
You're listening to *On the Frontlines of ATTR-CM* on ReachMD. And now, here's your host, Dr. Steve Jackson.

Dr. Jackson:
You're listening to *On the Frontlines of ATTR-CM* on ReachMD. I'm Dr. Steve Jackson. Today, we'll be discussing a secondary analysis of the HELIOS-B trial. This analysis looked at the effects of vutrisiran on cardiac structure and function in patients with transthyretin amyloidosis with cardiomyopathy, or ATTR-CM for short. And joining me today for this discussion is Dr. Karola Jering, who's a cardiologist at Brigham and Women's Hospital in Boston, and a co-author of this analysis.

Dr. Jering, thanks for being here today.

Dr. Jering:
Thank you so much for having me. It's such a pleasure.

Dr. Jackson:
So, before we dive into the data, Dr. Jering, can you give us a quick background on HELIOS-B? Who was enrolled, what was tested, and what did the main trial show clinically? And then where does this secondary analysis fit in?

Dr. Jering:
HELIOS-B was a double-blind, randomized, placebo-controlled trial that tested the efficacy and safety of vutrisiran dosed at 25 milligrams subcutaneously every 12 weeks versus placebo in patients with ATTR-CM. Vutrisiran is an RNA interference therapeutic agent that targets both wild-type and variant TTR messenger RNA in the hepatocyte for degradation, and then very rapidly knocks down circulating concentrations of the amyloidogenic TTR protein.

HELIOS-B involved patients between 18 and 85 years of age with either wild- type or variant ATTR-CM, elevated concentrations of NT-proBNP, and a six-minute walk test distance of greater than 150 meters. Baseline use of tafamidis was permitted. Key exclusion criteria were advanced disease as manifested by New York Heart Association functional class four or functional class three with a next stage of three, EGFR of less than 30, and prior use of TTR-lowering therapies.

So what did HELIOS-B show? In HELIOS-B, vutrisiran significantly reduced rates of all-cause mortality and recurrent cardiovascular events among patients with ATTR-CM compared with placebo, and it also preserved functional status and health-related quality of life.

In this secondary analysis, we specifically looked at the effects of vutrisiran on echocardiographic measures of cardiac structure and function, because we use echocardiography a lot in these patients, both for diagnosis and also as a serial imaging tool in these patients for surveillance.

Dr. Jackson:
And for some additional background, why are echo measures like wall thickness, strain, and filling pressures so helpful for tracking progression in ATTR-CM?

Dr. Jering:
When we think about the pathophysiology, ATTR-CM is caused by extracellular accumulation of misfolded TTR in the form of amyloid fibrils in the heart, and that leads to restrictive physiology, conduction disease, arrhythmias, and heart failure.

An infiltration of the myocardium with amyloid fibrils also underlies the characteristic echocardiographic findings that we're used to:

increased ventricular wall thickness, diastolic dysfunction with elevated filling pressures, biatrial enlargement, decreased global longitudinal strain, or GLS, with relative apical sparing, and, at advanced stages, false impairment, left ventricular ejection fraction, and RV systolic function.

In cross-sectional imaging studies using cardiac MRI, a greater burden of amyloid, as measured by ECB and LG has been correlated with more substantial abnormalities in cardiac structure and function—so greater wall thickness, LV mass, more advanced diastolic dysfunction, and also more advanced RB and LV systolic dysfunction.

Now, in clinical practice, it's difficult to image patients serially with cardiac MRI for obvious reasons, but we can easily use echocardiography to track our patients longitudinally and to monitor for disease progression there.

We know that ATTR-CM is a progressive disease and in prospective cohort studies, that has been characterized in echocardiography by gradual increases in LV wall thickness and progressive deterioration in LV systolic and diastolic function. As amyloid infiltrates the myocardium, it distorts normal tissue architecture and also increases chamber stiffness.

Dr. Jackson:
For those just tuning in, you're listening to *On the Frontlines of ATTR-CM* on ReachMD. I'm Dr. Steve Jackson, and I'm speaking with Dr. Karola Jering about the effects of vutrisiran on cardiac structure and function in patients with ATTR-CM.

So, Dr. Jering, with that helpful context in mind, let's dig into the findings, starting with structure. What did you take away from the changes in left ventricular wall thickness and mass index with vutrisiran versus placebo over 30 months?

Dr. Jering:
So, as I mentioned, amyloid burden is correlated with LV wall thickness and mass index. And here, in the placebo group in HELIOS-B, mean LV wall thickness and LV mass index increased from baseline to 130. However, treatment with vutrisiran attenuated these increases with a significant mean difference of negative 0.4 millimeters for mean LV wall thickness and negative 10.6 grams per meter squared for LV mass index.

Significant between-group differences weren't seen up until month 30 and during follow up. And that is not unexpected, knowing that changes in cardiac structure take time to evolve as amyloid deposits in the myocardium, and also knowing that most of the patients involved in HELIOS-B had wild-type disease. Those are patients that typically don't progress as quickly as patients with variant disease and particularly patients with a V122I or V142I variant.

Dr. Jackson:
All right. Now shifting to function, what did the trial show in terms of diastolic and systolic performance?

Dr. Jering:
So diastolic dysfunction is truly a hallmark of ATTR-CM and plays a crucial role in disease pathophysiology and evolution. In the placebo group, diastolic function deteriorated during follow-up. In contrast, vutrisiran significantly improved several indices of diastolic function, including the e-prime velocity, the E to E prime, and E to A ratios, with significant defenses of 5.5 millimeters per second for the lateral e-prime velocity, negative 2.0 for the E to e-prime ratio and negative 0.3 for the E to A ratio. The effects of vutrisiran on the diastolic function emerged early and was statistically significant between group differences. For E to E-prime, for example, it was observed as early as 12 months, and that's earlier than we would expect from the time course of the affecting of LV structure.

I should also mention that we typically think of the left atrium when we think about diastolic function as the key measure of the chronicity of elevations and filling pressures. In HELIOS-B, the left atrium enlarged in both treatment groups, and vutrisiran did not significantly alter left atrial size compared with placebo.

Now in ATTR-CM, the left atrium is heavily infiltrated with amyloid, and it becomes less compliant and less plastic. That may limit its ability to remodel in response to rising filling pressures. Subsequent analyses that were also presented at a AHA showed that left atrial strain, which is a more sensitive measure of left atrial function, was favorably affected by vutrisiran. So, in follow-up, vutrisiran attenuated bursting and left atrial strain compared with placebo.

Now, switching gears, if you want to talk about left ventricular systolic function, which is an important independent predictor of mortality in patients with ATTR-CM, as expected in a patient cohort with a progressive disease, LV systolic function deteriorated during follow-up. However, vutrisiran significantly and consistently attenuated declines in LV systolic function—significant between-group differences of two percent for reluctant to ejection fraction, 1.2 percent for absolute GLS, and 4.1 millimeters for LV stroke volume. It also attenuated declines in RBS prime in 30 months by essentially attenuating deterioration in RV systolic function as well.

Dr. Jackson:

Thank you. From my understanding, a sizable proportion of patients were on tafamidis at baseline. Were these structural and functional benefits still observed in that context?

Dr. Jering:
Yeah, that's a really good point. In HELIOS-B, 40 percent of patients were using tafamidis at baseline, and in patients who were not using tafamidis at baseline, an additional 22 percent started using it during follow-up. In the baseline tafamidis subgroup—so the 40 percent of patients using tafamidis at baseline—the treatment effects of vutrisiran were broadly consistent, although the analysis were really underpowered to evaluate treatment differences in the smaller subgroup.

Dr. Jackson:
And before we wrap up, Dr. Jering, let's zoom out for a moment. How do these imaging findings help explain the clinical outcomes that we saw in the HELIOS-B reductions in mortality in cardiovascular events?

Dr. Jering:
Echocardiographic measures of LV systolic and diastolic function have been shown to be independent predictors of all-cause death among patients with ATTR-CM. Knowing that vutrisiran had beneficial effects on outcomes, and also beneficial effects on cardiac function, we wondered how the favorable changes in cardiac structure and function with vutrisiran were associated with clinical outcomes.

And that's where we did a secondary analysis, particularly looking at how it changes in cardiac structure and function by 18 months poorly with outcomes. And here, we saw that, similar to the overall analysis, at 18 months, vutrisiran significantly, attenuated declines in both left and right ventricular systolic function and improved diastolic function. And changes in LV and RV systolic function in 18 months were related to the primary composite outcome and to all-cause death.

So, for example, in a landmark analysis, looking at outcomes occurring after 18 months a one-point percent worsening in absolute GLS was associated with a seven percent increased risk of the primary composite outcome. Similarly, a five percent-point decline in left ventricular ejection fraction was associated with a 12 percent greater risk, and a one centimeter per second decline in RBS Prime was associated with an 18 percent greater risk of the primary composite outcome.

Changes in diastolic function, though, were not significantly associated with clinical events occurring after 18 months. So these findings suggest that the clinical outcome benefits with vutrisiran in patients with ATTR-CM may at least, in part, be mediated by its favorable effects on echocardiographic measures of cardiac function.

Dr. Jackson:
That's a great perspective for us to think on as we come to the end of today's program. I want to thank my guest, Dr. Karola Jering, for joining me to discuss the impacts of vutrisiran on cardiac structure and function in ATTR-CM patients. Dr. Jering, it was great having you on the program.

Dr. Jering:
Thank you so much for having me. It was an absolute pleasure.

Announcer:
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