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The Clinical Weight of TTR: What the Latest Data Reveal

#### Dr. Masri:

Emerging data on transthyretin and amyloidosis, or ATTR, have been presented recently, including findings from the Heart Failure Association of the European Society of Cardiology meeting, and also data were presented from the UK Biobank. So let's explore the clinical implications of some of these data that have focused on acoramidis as a transthyretin-stabilizing therapy, and the association between baseline TTR levels as well as comorbidities. And then finally, some strategies for integrating insights into community-based patient care. This is CME on ReachMD, and I'm Dr. Ahmad Masri.

# Katie:

And I'm Dr. Rola Khedraki.

Ahmad, I understand that there were some interesting presented recently at the annual meeting of the Heart Failure Society of ESC in Belgrade. Serbia. What do clinicians need to know?

# Dr. Masri:

Indeed, lots of data have been presented. And the interesting thing is that the European Society of Cardiology, the Heart Failure meeting, as well as American College of Cardiology meeting, happened back-to-back, and lots of data were included in both of these meetings. One I think in particular that we were interested in and we also worked on is the association between acoramidis treatment and the lower incidence of atrial fibrillation or atrial flutter in patients with transthyretin cardiomyopathy.

So this was a post hoc analysis from the ATTRibute-CM trial, which is a trial of acoramidis versus placebo in these patients. And so what was new in this story is that patients with acoramidis who at baseline did not have atrial fibrillation as compared to placebo, there was reduction in the incidence of having cardiovascular hospitalization that were due to atrial fibrillation or atrial flutter. Specifically, this happened in about 3.7% of patients in the acoramidis group compared to 5.4% of patients in the placebo group, and that's a relative risk reduction of about 33%. Similarly, if we want to look at the annual frequency of CV hospitalizations related to AFib, that annual frequency difference was 0.02 compared to 0.03 with placebo. And that translates to about 40–45% relative risk reduction as compared to placebo.

And so there are important questions there. As should we start to think about atrial fibrillation as a modifiable endpoint in patients with transthyretin cardiomyopathy? Does it track with the cardiomyopathy in heart failure, or is it on its own a separate entity? And we should think about that.

And this is a very common problem in transthyretin amyloidosis, and it's associated with a lot of morbidity as well. And as such, we really should pay more attention to it. So this is really great to see that the treatment that we use nowadays approved, for example, in the United States for that indication, can result in that.





Another analysis that I thought was pretty interesting is that where acoramidis improved serum TTR level in patients with wild-type or variant transthyretin cardiomyopathy. And these were results also from the ATTRibute-CM trial. The interesting piece there is that we sometimes don't really focus too much on, within the trunk, the phenotype itself. How do variant and wild-type patients respond? And this analysis has shown that the patients response were consistent across different types of the transthyretin cardiomyopathy.

In fact, even though the numbers are small, it was shown that with acoramidis you have more increase in your serum TTR concentration as a percentage from baseline when it comes to patients with variant disease. And in theory, if you have the same degree of stabilization, this is somewhat expected in variant disease, knowing that it's more destabilized compared to wild-type.

And so the takeaway here is that acoramidis does work consistently across wild-type patients and variant patients. And compared to placebo, this is being consistent, and variant patients are deriving as much benefit as wild-type as well, if sometimes not even more. The numbers are small. So if we would want to focus more on the variant disease population, we might require secondary studies to focus on that. But ultimately, for now, what we can say is that there is no heterogeneity of effect, and patients are deriving benefit across the board there from this treatment.

And finally, another analysis that we looked at was the effect of acoramidis on all-cause mortality, cardiovascular hospitalization, and NT-proBNP in patients with variant transthyretin cardiomyopathy. And this is again results from the ATTRibute-CM trial.

And I think this is important, because we always think about variant TTR cardiomyopathy as being a more aggressive form of the disease as compared to wild-type, even though the evidence out there is mixed. But what we're trying to show here, and what we hope to see, is that with accramidis, those treatment effects as well as the effect size, is similar. And that's what we have seen—is that the effect size of accramidis treatment in variant patients is similar on all-cause mortality or CV hospitalization, all-cause mortality by itself, and first cardiovascular hospitalization by itself as well, and then on NT-proBNP, obviously, as compared to placebo.

And what's interesting is that even though this is a small subgroup, when it compares acoramidis subgroup was 39 patients, and then placebo subgroup was 20 patients; yet with having a small subgroup, the effect size was consistent, and the point estimate was even stronger in terms of treatment effect compared to the wild-type population. And so that's very reassuring, I think, in our practice, that these patients are really deriving benefit from being on acoramidis having variant disease or having wild-type disease there.

And so I know I've spoken a lot about a lot of these new investigations. One recent paper that I was also a co-author on, where we looked at the level of TTR and its association with outcomes in the ATTRibute-CM trial as well, this was published in the Journal of American College of Cardiology. Dr. Khedraki, what are the key takeaways for clinicians from that paper?

Thank you for your input here. I can tell you from my perspective really what's powerful for me is that we are inching closer to translating a biomarker where we can use it to understand outcomes of patients. And so that's really important, because it's a step forward in trying to personalize how we deliver these therapies to patients, instead of only having one drug, one option, one treatment, and you don't know what response looks like. These data really double inch us closer to understanding how response looks like. And the fact that this response, at the unit level is associated with outcome, is really meaningful to me.

#### Katie:

Now, let's take a closer look at the insights from the UK Biobank database, which were presented recently at the annual meeting of the Peripheral Nerve Society in Edinburgh, Scotland.

### Dr. Masri:

Great, yeah. This is an investigation that is observational from the UK Biobank. Data in the UK Biobank is about 500,000 subjects in there. And many of them are healthy. They participate in the UK Biobank. And about 50,000 of them or so have proteomics analysis done using the Olink platform. And so that was leveraged to understand the proteomic landscape in patients with TTR amyloidosis, but also patients without TTR amyloidosis in that subset.

And what transcribed from there is that if you have a naturally occurring or spontaneously occurring low TTR level, you have an association with a higher burden of chronic diseases that are important. That includes vascular disease such as peripheral vascular disease, cerebrovascular disease, having strokes and TIAs and whatnot, but also include cognitive issues related to cognitive impairment, dementia, and Alzheimer's disease.





Obviously, this is looked at both in the TTR population, which you would expect to have lower serum TTR from destabilized disease to begin with, but also in the overall population. And that idea is important, because what we're trying to understand is that why do people spontaneously without having, for example, disease—why do they have lower levels of TTR? What are the roles of TTR in the general non-disease population and also in the disease population. And what kind of investigations do we need to actually focus on down the road to understand the effect of manipulating TTR levels? Because it's important to realize that when we treat patients with stabilizers, we're increasing the TTR levels in disease patients. When we treat patients with a silencer or a knockdown agent, we are reducing the TTR level.

Now, clinical trials have been conducted for many years and have not really shown an adverse effect related to these strategies. But what some of these observations argue is that we should continue to work hard to generate more and more data to understand over 5 and 10 and 15 years what is happening to patients as we are manipulating these TTR levels.

#### Katie:

Ahmad, thinking about all these results, how can learners apply this in their clinical practice?

#### Dr. Masri:

I think the way to think about this in clinical practice is the fact that, right now, we have multiple medications to treat transthyretin amyloidosis cardiomyopathy that are approved. And depending where you are, not all of these are approved.

But let's talk about the United States. Acoramidis, tafamidis, and vutrisiran are approved for the treatment of transthyretin cardiomyopathy. And I think what's important from our perspective is to have more data and to have more investigations done from these trials, because we really don't have necessarily head-to-head comparisons between these—

Yeah. So that's a great question, Dr. Khedraki. I think the way to think about this is really the sequence of the different investigations that we went through. We know that accramidis now is approved for the treatment of transthyretin amyloid cardiomyopathy in many geographic jurisdictions, including the United States. And so right now, we are using it for the treatment of these patients.

The presented data give you more evidence in terms of these subpopulations that one is focusing on in their clinical practice. That includes patients who are at risk of atrial fibrillation, or patients who are variant disease compared to the wild-type patients, and also patients with different severity of their disease at baseline. All of these different populations, we now know that if you focus even on these smaller subgroups, that accramidis has been—and is—associated and shown to be leading to improved outcomes.

And as such, I think such data give you comfort and reassurance, as well as push you more towards having frank discussions with the patients on the use of one agent versus another based on what data you have at hand.

#### Dr. Masri:

Before we wrap up, let's offer a final take-home message. What do you hope our listeners will leave with today?

So from my perspective, I think it's important to understand that atrial fibrillation is an important event in patients with transthyretin amyloid cardiomyopathy, and we are working on preventing that. And we now have some data to suggest how this can potentially be achieved. So that's really one take-home message.

The second take-home message is that variant patients tend to have more destabilized TTR, and treatment with accramidis as a TTR stabilizer has led to similar magnitude, if not better magnitude, of benefit compared to the wild-type patients as well. And so that's going to help us in how we discuss with patients in daily practice.

Somewhat repetitive from what we've said before. So let me—let me rethink that answer for a second there.

So that's great. For me, the take-home message is that we really need to continue our investigations into the different treatments that are available for the treatment of transthyretin amyloid cardiomyopathy, as well as continue our investigation into the subpopulations of that disease. As you know, Dr. Khedraki, like a lot of these patients are not necessarily homogenous. There are different types of disease, there are different severity of disease, and data such as what we talked about today really provide us with more evidence to





understand how do these treatments apply to these subsegments of the population of patients with TTR amyloidosis.

And that's all the time we have today. I want to really thank our audience for listening in.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Ahmad Masri, and we are discussing recent results in transthyretin amyloid cardiomyopathy.

Emerging data on transthyretin amyloidosis have been presented recently, including findings from the Heart Failure Association of the European Society of Cardiology meeting and the UK Biobank.

Let's explore the clinical implications of acoramidis therapy, the association between having a baseline low TTR levels and comorbidities, as well as strategies for integrating insights into the community-based patient care. This is CME on ReachMD, and I'm Dr. Ahmad Masri.