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### ATTRIBUTE-CM Trial Updates: Long-Term Outcomes With Acoramidis

#### Announcer:

You're listening to *On the Frontlines of ATTR-CM* on ReachMD. And now, here's your host, Ryan Quigley.

#### Ryan:

This is *On the Frontlines of ATTR-CM* on ReachMD. I'm Ryan Quigley, and joining me to discuss the latest updates from the ATTRIBUTE-CM trial is Dr. Kevin Alexander. He's an Assistant Professor of Cardiovascular Medicine at Stanford University School of Medicine, and he specializes in the management of advanced heart failure and transplant cases.

Dr. Alexander, thank you so much for being here today.

#### Dr. Alexander:

Thanks for having me, Ryan.

#### Ryan:

So, for some background, Dr. Alexander, can you briefly remind us what the ATTRIBUTE-CM trial set out to evaluate?

#### Dr. Alexander:

The ATTRIBUTE-CM study wanted to look at the efficacy of a transthyretin stabilizer called acoramidis in a population of ATTR cardiac amyloid patients. And this included both wild-type and hereditary, or variant, ATTR patients. They were initially followed over a 30-month period and were randomized to acoramidis versus placebo. The primary endpoint was a composite that included mortality, cardiovascular hospitalization, a six-minute walk test, and a natriuretic peptide biomarker. That study has been subsequently followed up in open-label extension where patients had the option to cross over to acoramidis and be followed longitudinally. And data up to 42 months at this point have been reported.

#### Ryan:

Thank you for that detailed breakdown. And with that in mind, what were the primary goals of the open-label extension?

#### Dr. Alexander:

As we see these effective therapies emerge for ATTR, patients are living longer, and it's important to understand how they do over an extended period of time. I think the other thing that the open-label extension study helps us with is understanding how important it is to start treatment early because one thing we observed in the open-label extension was those patients who were on placebo and then transitioned over to acoramidis for the extension never quite caught up to the group that was on acoramidis continuously. So, I think that further highlights the importance of the early diagnosis and early treatment to have the best outcomes for these patients.

#### Ryan:

Thank you very much for that. And for those just joining us, this is *On the Frontlines of ATTR-CM* on ReachMD. I'm Ryan Quigley, and I'm speaking with Dr. Kevin Alexander about updates from the ATTRIBUTE-CM trial on acoramidis.

Now, Dr. Alexander, if we continue to review the newest findings here, one notable subgroup from the trial includes patients with the p.V142I variant, which we know is more common among Black Americans. What did the trial reveal about the efficacy of acoramidis in this group?

#### Dr. Alexander:

So, as I mentioned earlier, there's two big subtypes of ATTR: wild type and variant. The latter is caused by a point mutation in one or both copies of the transthyretin protein, and this can lead to an inherited form of the disease.

People with hereditary ATTR tend to have a more aggressive course of disease and tend to present at an earlier age. And we know they tend also to have worse outcomes overall. There's an overall need for effective therapies for ATTR, but in particular, these variant patients have a lot of disease burden. There's been more than a hundred variants that have been described to lead to hereditary ATTR. There's several that are most common in the US, the most common being the V142I variant that you mentioned, which is carried by up to four percent of Black individuals. So we're talking over a million carriers in the U.S. alone.

So this is something that's been shown in a number of studies to lead to disproportionate burden of heart failure among Black individuals. So from a public health standpoint, understanding how ATTR therapies work in this subpopulation is important.

We recently published in *JAMA Cardiology* the subgroup analysis for not only variant patients in ATTRibute-CM, but specifically, the V142I population. What we found is there's consistent clinical benefit across the variant group and the V142I group.

When we look at the 42-month extension data, we see that there's a 69 percent relative risk reduction in all cause mortality as well as a composite of CV mortality and hospitalization.

The important caveat is that it's a relatively small group of patients and it wasn't a pre-specified endpoint, so I would say that this is data that needs to be further validated in real world evidence, but it's certainly encouraging to see that degree of clinical benefit in this high-risk group.

**Ryan:**

I can see why there's some excitement around that result in this study. And so what does the latest analysis tell us about the tolerability of acoramidis over this extended treatment period?

**Dr. Alexander:**

I think the good news is in the original 30-month study, safety was very good. There wasn't much in the way of significant safety events. And we see that pattern continue through 42 months. So as patients live longer with ATTR and are exposed to treatment for longer periods of time, I think it's reassuring to see that there's no longer-term safety effects that we observed.

**Ryan:**

Now, Dr. Alexander, looking ahead, what's next in exploring acoramidis and other potential treatment options in ATTR-CM?

**Dr. Alexander:**

For acoramidis specifically, now that it's been available for clinical use a little over a year now, I think seeing what our collective experiences are at amyloid centers with acoramidis will be important. So, I think real-world evidence generation to understand how acoramidis as well as other therapies perform in a diverse group of patients, which oftentimes is a broader range of patients than what we see in clinical trials, will be important. In addition, understanding how these therapies can be used in combination or isolation is something that, now that we have multiple therapies, needs to be further explored.

In terms of things that are on the horizon, there's a number of clinical trials for another mechanism of action for treatment: the so-called TTR deleter class, which are monoclonal antibodies that could potentially bind to the transthyretin and promote its clearance from the heart and other places. I think this is an exciting potential mechanism of action because what we know about the transthyretin stabilizers, as well as silencers or knockdown agents, is that they work predominantly by reducing the production of new amyloid from forming. But patients and physicians always ask, "What about the amyloid that's already deposited in the heart in other places?" And so if these depleters are effective at removing amyloid, they could be a potentially important complement to the therapies that we currently have.

**Ryan:**

I just want to thank my guest, Dr. Kevin Alexander for joining me to discuss the ATTRibute-CM trial and implications for patient care. Dr. Alexander, thanks so much for doing this. Really appreciate your time.

**Dr. Alexander:**

Thanks for having me, Ryan.

**Announcer:**

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