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RNAi Therapeutics in ATTR-CM: Clinical Evidence and Potential Impacts

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

Dr. Ramnarine:
Welcome to *On the Frontlines of ATTR-CM* on ReachMD. I'm Dr. Shelina Ramnarine, and joining me to discuss the impacts of RNA interference therapeutics in transthyretin cardiac amyloidosis, or ATTR-CM, is Dr. Chadi Alraies. He's a Clinical Associate Professor at the Wayne State University School of Medicine in Detroit as well as the Director of Interventional Cardiology Research at DMC Heart Hospital. He is also co-author of a recently published systematic review and meta-analysis on this subject.

Dr. Alraies, it's great to have you here today.

Dr. Alraies:
Thank you for having me.

Dr. Ramnarine:
So, for some background, Dr. Alraies, how does RNA interference therapy work in ATTR-CM, and why is turning down transthyretin production so important in treating this disease?

Dr. Alraies:
That's a pretty important question. RNAi therapeutics are designed to target transthyretin, or TTR, messenger RNA in hepatocytes and trigger degradation via the RNA-induced silencing complex, which reduces hepatic production of circulating TTR protein. With less circulating TTR available, there is less substrate to misfold, aggregate, and deposit as amyloid fibrils in the myocardium, which is central to slowing and potentially altering the disease trajectory in ATTR cardiomyopathy.

Dr. Ramnarine:
So, in your review, you noted that RNA interference therapeutics substantially improved survival for ATTR-CM patients. Can you tell us about how you came to this finding and what it may mean for clinical practice?

Dr. Alraies:
The meta-analysis that we did was a PRISMA-style systematic review. We pulled available randomized evidence comparing RNAi therapy versus placebo in ATTR cardiomyopathy and found an overall signal consistent with improved survival alongside parallel improvement in clinical status and biomarkers.

Clinically, that combination of survival and function and patient-reported health status supports RNAi as more than symptom control. It suggests a disease-modifying effect that could justify earlier use and more systematic deployment once eligibility access and pathways are established.

Dr. Ramnarine:
So, let's talk now about functional decline for a moment. How do you interpret changes in measures like exercise tolerance or six-minute walk distance when evaluating the impact of these therapies?

Dr. Alraies:
In ATTR cardiomyopathy, patients often experience predictable progressive functional decline. So, when evaluating RNAi therapies, I interpret functional endpoints like six-minute walk distance in two clinically meaningful ways. One: prevention of deterioration and stabilization versus the expected drop in placebo usual care can be a major win. And two: absolute improvement is valuable, but even

modest between group differences can matter if they align with how patients feel and function and the downstream event. This is why the six-minute walk test is commonly paired with health status instruments, like the KCCQ—to confirm that functional changes translate to lived benefit.

Dr. Ramnarine:
For those just tuning in, you're listening to *On the Frontlines of ATTR-CM* on ReachMD. I'm Dr. Shelina Ramnarine, and I'm speaking with Dr. Chadi Alraies about the role of RNA interference therapeutics in ATTR-CM management.

Now, Dr. Alraies, beyond measurable cardiac parameters, quality of life is central in ATTR-CM. What do we know about how RNA interference therapy impacts the day-to-day experiences of patients?

Dr. Alraies:
That's a good question. The review concludes that RNAi therapy is associated with improved quality of life versus placebo in ATTR cardiomyopathy. In practice, this typically shows up in domains in patient care about less limitation with walking and daily tasks, less fatigue and dyspnea burden, and better overall perceived health captured in cardiomyopathy-specific patient-reported outcome measures—commonly the KCCQ metric in modern ATTR cardiomyopathy trials.

Dr. Ramnarine:
So, your review looked at BNP levels and global longitudinal strain with RNA interference therapy. Could you tell us what you learned about this?

Dr. Alraies:
The meta-analysis reported a marked reduction in BNP and improvement in GLS with RNAi therapy compared with placebo. Both are considered high value signals in ATTR cardiomyopathy. BNP and NT-proBNP reflect myocardial wall stress and correlate with congestion and prognosis, and reduction of this marker supports improvement in hemodynamics and clinical status. GLS is a sensitive marker of LV systolic function and amyloid, often abnormal before ejection fraction fall. An improvement or stabilization suggests less progressive myocardial impairment, though GLS remains load dependent and should be interpreted alongside volume status, blood pressure, and imaging context.

Dr. Ramnarine:
So, as we come to the end of the program, Dr. Alraies, let's put all of this into context. What do these findings tell us about the potential of RNA interference therapeutics, and how do you see them being effectively integrated into clinical practice?

Dr. Alraies:
Taken together—survival signal, functional and quality-of-life improvement perseverance, and biomarker and GLS improvement—the findings support RNAi therapeutics as a credible disease-modifying pillar for ATTR cardiomyopathy, specifically because they directly reduce the upstream driver, which is circulating TTR.

Integrating this into clinical practice, realistically, looks like, number one, earlier identification and referral because benefit is greater when myocardium is less advanced. Two, clear selection and sequencing alongside stabilizers and heart failure therapies which, with multidisciplinary amyloidosis programs, standardizing the pathway is critical. And three, structured monitoring, including clinical status, NYHA class, six-minute walk, PROs, KCCQ-style metrics, biomarkers like BNP and NT-proBNP, echo strain plus class-specific safety consideration, and supportive care like vitamin A consideration with ATTR knockout therapies.

Dr. Ramnarine:
Those are great insights for us to think about as we come to the end of our discussion. I'd like to thank my guest, Dr. Chadi Alraies, for joining me to discuss how RNA interference therapy fits into the ATTR-CM treatment landscape.

Dr. Alraies, thanks for joining us today.

Dr. Alraies:
Thank you for having me.

Announcer:
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