Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/on-the-frontlines-of-attr-cm/redefining-attr-cm-care-in-the-age-of-targeted-therapy/49035/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Redefining ATTR-CM Care in the Age of Targeted Therapy

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

Dr. Jackson:
This is *On the Frontlines of ATTR-CM* on ReachMD, and I'm Dr. Steve Jackson. Today, I'm joined by Dr. David Rind to discuss a summary from the Institute for Clinical and Economic Review's Midwest Comparative Effectiveness Public Advisory Council. The summary explores clinical effectiveness, cost effectiveness, and policy implications of disease-modifying therapies for transthyretin amyloid cardiomyopathy, or ATTR-CM. Dr. Rind is the Chief Medical Officer for the Institute for Clinical and Economic Review and a co-author of the summary we'll be discussing today.

Dr. Rind, welcome to the program.

Dr. Rind:
Thanks so much.

Dr. Jackson:
To start us off, Dr. Rind, can you give us a brief overview of ATTR-CM and why the emergence of disease-modifying therapies represents such a pivotal shift in care?

Dr. Rind:
Sure. So transthyretin—which, if you're as old as I am, used to be called prealbumin—is a protein that can misfold, for reasons people don't completely understand, and deposit in tissues. And that's one of the forms of amyloidosis. And that misfolding can occur either with normal transthyretin or with mutated transthyretin. And both forms of this occur in the US population—there's actually much more of the normal form of misfolding occurring as people get older and depositing in tissues.

And this can cause various problems, but among the most common problems it causes are neuropathies and cardiomyopathy—amyloid cardiomyopathy. And you also see amyloid cardiomyopathy from other forms of amyloid, particularly plasma cell dyscrasias that produce too much light chain, and that forms amyloid and deposits in the heart. When you get amyloidopathy of the heart, what happens is the heart stiffens, and you get dysfunction of the heart muscle as a result. And you also can get arrhythmias and other problems of the heart. And, as with any cardiomyopathy, people end up debilitated, short of breath, unable to do what they used to be able to do, and they die of this.

If you go back before about 2019, when the first stabilizing agent came along, which was tafamidis, people just treated this as you would any other cardiomyopathy, because there was no real specific therapy that at least people were agreed on giving at that point. And so you were doing heart failure medications like ACE inhibitors and all the goal-directed medical therapies you might do, but there was nothing that really altered what was going on with the amyloid itself. But stabilizing agents came along and they help prevent the shift from correctly folded to misfolded versions of transthyretin, and that's helpful. And then, more recently—and at the time we were doing this report—coming along were RNA silencing drugs that actually decreased production of transthyretin.

And this has had big effects on our ability to treat ATTR-CM and to manage ATTR-CM, which I'm sure we'll get into, but the fact that we have a treatment actually means that people now go look for this in a way that they mostly didn't bother to.

Dr. Jackson:
So the summary evaluated tafamidis, acoramidis, and vutrisiran, but noted important differences across trials. What stood out to you

most when examining their clinical effectiveness?

Dr. Rind:
So I think there are probably two big things. One is, tafamidis as it came along was in this place where we weren't looking hard early for ATTR-CM. And so you weren't finding early cases. You were finding more advanced, more symptomatic cases, and that was true of who was studied in the trial of tafamidis and the benefits that were seen.

By the time acoramidis was being studied, there was both an earlier population, and some of the people were already on tafamidis. And acoramidis had a harder time showing benefit, probably because the patients weren't as sick, and so you weren't going to have as many events in a trial.

And what's notable is that the study of vutrisiran—this RNA silencing drug with different mechanism of action—despite the fact that it, again, was in this earlier population—and, in fact, 40 percent of the patients were on tafamidis, so lots of people on good therapy as we understood it at that point—it still showed dramatic benefits of vutrisiran. And it didn't seem to matter much whether you were on tafamidis or not, you got the same relative benefit when vutrisiran was added, and we thought that was quite striking.

Dr. Jackson:
Despite favorable safety profiles across all three therapies, you described several uncertainties in the evidence base. Where do you think clinicians should be most cautious when interpreting these results?

Dr. Rind:
So I do think that what I was just describing is maybe the greatest uncertainty: what happens when you get to earlier and earlier patients when, previously, the studies will have been further down the road. So you might expect, and it might well be true, that treating very early gets you greater benefits than treating later, but we don't really have strong evidence for that yet.

I think the other big one—and it's really big, because I'm sure we're going to talk about the price of these agents—is whether you should be doing combination therapy. And our sense was that if you were on tafamidis, it was clear that you got additional benefit from adding vutrisiran. That doesn't prove that combination therapy is better than single therapy with vutrisiran, but we don't actually know whether vutrisiran alone, tafamidis alone, or a combination of a stabilizing agent with an a silencing agent like vutrisiran is the best option.

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. David Rind about the effectiveness and value of disease modifying therapies for ATTR-CM.

So, Dr. Rind, let's shift gears now and talk about the economic perspective. Your modeling found that at current pricing, these therapies greatly exceed commonly accepted cost effectiveness thresholds. Can you walk us through what drove those results?

Dr. Rind:
Sure, and I know that most clinicians aren't that used to cost effectiveness, in the US at least. So what we're looking at here is saying that when we think about how much you should pay for a drug, it matters how much it helps people, and also how many costs it offsets. So, does it extend life? Does it make people feel better? Are there costs that you don't have to pay because you're paying for this drug, like hospitalizations for heart failure? And I can tell you that these drugs do that. They make you feel better. They extend life and they offset some other costs.

And the expectation is not that a drug will save money—it's reasonable to pay money to get more life and better health. So the cost offsets don't have to be more than the cost of the drug, but we're talking about drugs that ICER estimated, at least for the stabilizing agents—or acoramidis and tafamidis—might be worth as much as $39,000 a year. Now, the drug companies are all charging more and more and more every year for their drugs, but $39,000 a year, that's a lot of money. That's not nothing.

The actual prices for these drugs, the list price, for acoramidis is currently $244,000 a year. For tafamidis, it's $271,000 a year. People don't usually actually pay the list prices. They get discounts off those prices, and we have estimates of the net price. So currently—I was just looking at these numbers—for instance, the estimated net price for acoramidis is $189,000. So let's say that we think it's worth as much as $39,000 and you're paying $189,000. We might go, well, people are living longer and doing well. You're overpaying by about $150,000 per patient per year.

So, for one patient for one year, with that $150,000, you might consider, if we were just thinking about drugs, think about how much GLP-1s cost. You could have more than 40 patients on oral semaglutide for that price. And lots of people are having trouble getting oral semaglutide as insurance backs away from it, because it doesn't have enough money. And so if you overpay by that amount for one heart drug, you are failing to decrease cardiac events in more than 40 people by 20 percent. That's how much we know that semaglutide decreases cardiac events. You're losing health in the overall population. You're helping the people you're treating for ATTR-CM, but

because you don't have enough money anymore to pay for drugs for everybody—because we don't have infinite money in our health system—people are finding it harder and harder to get other drugs, and among those drugs or other cardiac drugs, drugs like the GLP-1, which really are cardiac drugs. Their biggest effect on health is in decreasing cardiac events, and people are finding those harder and harder to find.

Dr. Jackson:
And the panel ultimately concluded that evidence supports a net health benefit compared with no disease specific-treatment, but not superiority of one agent over another. How should clinicians interpret that nuance?

Dr. Rind:
In the absence of head-to-head trials, you have three agents that were studied in different populations. And when that happens, it can be hard to be certain.

I can tell you that my guess is that vutrisiran is better than the other two drugs. That would be my guess if I had to bet on it, but I'm not at all sure of that. I don't know what would happen if you ran a head-to-head randomized trial of vutrisiran against tafamidis against combination therapy. And particularly, when you're spending these amounts of money on a therapy, you'd like to know for sure, what's the best therapy and by how much is it the best? So I think that's what the panel was reflecting, and I think that we're right. We're not sure of these things and it would be great to have head-to-head trials.

Dr. Jackson:
And finally, Dr. Rinn, looking ahead, what are the most pressing research or policy priorities to ensure patients with ATTR-CM have both access and sustainable care?

Dr. Rind:
I think there are a few things. The first is those head-to-head trials I was talking about. The second I also was talking about, which is the prices need to come way down, so that there will be better access, if prices are lower. If combination therapy is the way to go, insurance companies that are already way overpaying for these drugs are not going to make it easy to do combination therapy. And then payers try to handle that by making clinicians and patients do prior approval, which everyone hates and is just a waste of resources that provides no additional health.

I would also say that we need to really understand on the research front whether treating much earlier is beneficial, whether we should be looking for this condition earlier with the thought that we could prevent cardiomyopathy, we could prevent death, or we could prevent neuropathies, to the extent they're happening in these same patients.

One other big policy thing that came out is that there just aren't a lot of cardiologists who are experts in treating or diagnosing ATTR-CM. And this may be a much more common condition than we understand, so we need to both think about how to make sure we have enough physicians who know what they're doing to diagnose and treat the condition, and if we don't currently, we should be thinking about policies like we had during COVID, where you could do cross-state telehealth so that, at least, you could consult with an expert in this condition if there isn't one available to you locally.

Dr. Jackson:
With those key takeaways in mind, I want to thank my guest, Dr. David Rind, for joining me to discuss how emerging disease-modifying therapies are reshaping ATTR-CM care. Dr. Rind, it was great having you on the program.

Dr. Rind:
Thanks so much for having me.

Announcer:
You've been listening to *On the Frontlines of ATTR-CM* on ReachMD. To access this and other episodes in our series, visit *On the Frontlines of ATTR-CM* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!