Dr. Robert Page (00:08):

Hello everyone, and welcome to the American Heart Association's ATTR Closing the Knowledge Gaps in Transthyretin Cardiomyopathy podcast series. My name is Robert Page. I'm from the University of Colorado, and I'm going to be moderating this discussion today on the episode entitled Pharmacotherapy for Cardiac Amyloidosis. We are so fortunate today to have two distinguished guests that are not only at the forefront of cardiac amyloid, but also thought leaders within the field. So again, we are so thankful today to have Dr. Kittleson and Dr. Ambardekar. I would like it if both of you guys could introduce yourselves. So I'm going to start with you, Dr. Kittleson.

Dr. Michelle Kittleson (00:55):

I'm Dr. Michelle Kittleson. I'm a Heart Failure Transplant Cardiologist at Cedars-Sinai in sunny Los Angeles, California. And I also have the privilege of chairing two documents on cardiac amyloidosis, the 2020 AHA Scientific Statement, as well as the 2023 ACC Expert Consensus Decision Pathway Document.

Dr. Robert Page (01:16):

Awesome. Thank you so much. Dr. Ambardekar?

Dr. Amrut Ambardekar (01:19):

Thank you, Robert. So my name is Amrut Ambardekar. I'm an Advanced Heart Failure Transplant Cardiologist at the University of Colorado where I direct our Cardiac Transplant Program. And I've also been privileged to work with Dr. Kittleson on both of those amyloid statements, and look forward to this conversation.

Dr. Robert Page (01:37):

Excellent. Thank you so much. So let's turn directly to you, Dr. Kittleson. Let's just go ahead and just dive on in. Again, both of you have been at the forefront of pharmacotherapy with regards to this condition. Can you speak to the overall treatment recommendations and the role of specific disease modifying agents in the management of cardiac amyloid, and in particularly, going to throw in another question here, how has the pharmacotherapy really evolved over time?

Dr. Michelle Kittleson (02:10):

That is so great a question, and it's such an exciting time to be treating patients with cardiac amyloidosis because of so many simultaneous advances and our ability to diagnose and treat the condition. I remember being in medical school over two decades ago, and knowing amyloid existed, but not really caring about it because why did it matter if you diagnosed it? You couldn't treat it. Whereas now, we have very specific important disease modifying therapy that follows the pathophysiology of the condition. So the problem is you got the TTR protein that's produced by the liver. In a perfect world, that forms stable tetramers and goes to the body doing what it's supposed to do. But an imperfect world, that forms fibers that then deposit into tissue.

(02:49):

So there's different ways you could target it. You could stop the production of the TTR protein. And the most extreme example with liver transplantation, which used to be the only therapy. Next, you could have silencers that stop at the mRNA level. Then you can have stabilizers that keep it in the happy tetramer form so it doesn't form the fibers to get into the tissue, and then you could have disruption or resorption when it's actually in the tissue. So where are we? There are silencers that work on the mRNA

level. There are stabilizers that help keep it as tetramers. We are not at prime time yet when we think about sucking it out of the tissue and reversing the process.

(03:28):

So then if we're thinking about silencers versus stabilizers, what do we have that's shown beneficial in patients with cardiomyopathy TTR amyloidosis? What is FDA approved? And where it's added tafamidis? Tafamidis is a TTR stabilizer that has been shown to increase survival and reduce hospitalization and is the therapy for transthyretin cardiac amyloidosis. It stands to reason that the silencers would also be amazing, but we don't know that yet definitively from clinical trials. We know that in patients with the variant form and neuropathy, it can slow progression. There are ongoing trials to figure out the hard endpoints we care about, survival and cardiovascular hospitalization. So stay tuned. More to come in the next few years.

Dr. Robert Page (04:20):

Excellent. So again, thank you for highlighting the efficacy of these agents, but patients really worry about side effects. And so in particular, what do you see in your population that you've been managing?

Dr. Michelle Kittleson (04:33):

So tafamidis is really extraordinary. I think because it's such a focused targeted therapy, it stabilizes the tetramer. It doesn't do much else. So it is really extraordinarily well tolerated, and you don't have to monitor electrolytes or kidney function or liver function. You just set it and forget it. Now if you have a patient with the variant form and the neuropathy, you will partner, collaborate ideally with your friendly neurologist, to assist you in the prescription process. Patisiran is a little bit annoying. It's an IV every three weeks. Vutrisiran is better. It's subcutaneous every three months. So those are better options in that situation. You also need vitamin A supplementation because one of the things the TTR protein does is carry the vitamin A around the body. So if you're on a silencer, you need to give more vitamin A supplementation or the TTR protein can't do its job. But overall, when it comes to tafamidis, the only FDA-approved therapy for patients with transthyretin cardiac amyloidosis, it's extraordinarily well tolerated.

Dr. Robert Page (05:34):

Awesome. I know that's very helpful for our patients. So Dr. Ambardekar, I know, and I've had the pleasure of working with you, that you direct the Cardiac Amyloid Program here at the University of Colorado. Within your practice, when do you consider specific pharmacotherapy agents and in what order?

Dr. Amrut Ambardekar (05:56):

Yeah, that's a great question. So the first thing I like to differentiate are what are the actual supportive treatments versus the disease modifying treatments that Dr. Kittleson was talking about. So the supportive treatments are standard heart failure care, standard arrhythmia care. So if an amyloid patient has atrial fibrillation, we're doing rate control, rhythm control, those discussions. Anticoagulation is critical. Not a lot exciting there. For heart failure, there have been some new developments, so things such as SGLT2 inhibitors, aldosterone antagonists, as well as optimizing volume status with diuretics, and do use remote monitoring technology or implantable sensors to make sure people's volume status are controlled. So those are some of the new things that I would consider as supportive treatments for heart failure, and we do those things anyway. What's new, and I think what's exciting is Dr. Kittleson brought up are the disease modifying treatments.

(06:55):

So the first question I asked myself is, does this patient have wild type or what we used to call senile TTR amyloidosis, but really a non-hereditary version? And if they have wild type ATTR cardiomyopathy, there isn't a lot of discussion right now. There is one in only one approved treatment in the United States for wild type ATTR cardiomyopathy and that's tafamidis. So that is what we prescribe. If a patient has variant or mutant or hereditary or genetic, if they actually have a TTR mutation, the question that I ask myself is do I think this patient in front of me has mostly cardiomyopathy, mostly polyneuropathy or a mixed bag? And that's where, as Dr. Kittleson mentioned, it is critical to work with your friendly neurologist, someone who is used to seeing amyloid patient been used to sorting out whether somebody has significant polyneuropathy. If somebody has significant polyneuropathy, and that is really their main disease manifestation of their variant ATTR.

(07:57):

That's where I think we think about the TTR silencers and the patisiran, the vutrisiran, inotersen. There's three of them that are approved in the United States. I think vutrisiran, which is an every three month subcutaneous injection has some convenience features of it, that is what most neurologists are turning to for their first line for hereditary ATTR polyneuropathy. On the flip side, if somebody has variant or hereditary ATTR cardiomyopathy and that's their main manifestation and they really had real clinical heart failure, the treatment again, as Dr. Kittleson mentioned, is tafamidis. And that's the one that's approved in the United States right now. A lot of exciting things on the forefront. If we were having this conversation two or three or four years from now, we may have some different treatments that are coming about, but right now in 2023, that is how I approach things.

Dr. Robert Page (08:50):

Awesome. And I noticed that you alluded to this in terms of patient specific factors, but is there anything else that you take into account at the patient level when selecting pharmacotherapy?

Dr. Amrut Ambardekar (09:02):

Yeah, I think again, if you split it up into the supportive treatments versus disease modifying, the supportive treatments, absolutely. If somebody has volume overload and they also have comorbidities of CKD and may have proteinuria or they have diabetes, that's where you're leaning towards an SGLT2 inhibitor. If somebody is on big doses of loop diuretics and they're complaining about how big the potassium pills that they're taking in addition to the loop diuretics to keep their potassium balance in check, then an aldosterone antagonist has some benefits as well.

(09:34):

So I think that's where we're looking at what is the patient's volume status, what is their comorbidities? Are there medications that can do more than one thing at once? And oftentimes patients have some level of renal disease, some level of proteinuria, some level of diabetes, as well as their amyloid cardiomyopathy. And there's some agents that can do more than one thing with one agent. I think for the disease modifying treatments, it's really what disease do they have? Do they have wild type ATTR cardiomyopathy or do they have variant ATTR cardiomyopathy in which case it is tafamidis. If they have variant ATTR polyneuropathy, then it is a silencer.

Dr. Robert Page (10:12):

Nice. Thanks so much, Dr. Amrut Ambardekar. You brought up this issue of comorbidities and one of the issues that we run into within this patient population is atrial dysfunction and both atrial and ventricular

arrhythmias. So I'm going to turn to Dr. Kittleson. Dr. Kittleson, how to treat these various arrhythmias and when do you consider device therapy? Because that's also a big area to explore.

Dr. Michelle Kittleson (10:38):

Okay, so you're giving me all the hard questions. Fine.

Dr. Robert Page (10:41):

I'm so sorry.

Dr. Michelle Kittleson (10:44):

I'm ready for it. I can handle it. Okay, let's talk atrial arrhythmias to start with.

Dr. Robert Page (10:47):

Yes.

Dr. Michelle Kittleson (10:48):

Patients with cardiac amyloid doses have a high incidence of atrial fibrillation. They're generally old anyway and their atriums are all stretched and large as of this restricted physiology. What do you need to know? Number one, you will anticoagulate them regardless of their CHADS2-VASc score. Why is that? Because they have such a high risk of thromboembolism. Granted, you could argue their CHADS2-VASc score is probably high anyway because they're really old, but it doesn't matter. You're not even going to consider it. You're going to anticoagulate them.

(11:16):

Second thing. So that's the thromboembolic risk. Second, what about symptoms? Well, they might need rate control and you might want to give them an AV nodal blocker, like a beta blocker. On the other hand, they've got a fixed stroke volume and they're restrictive, so they might get really tired. It's a balance of a bit of lenient rate control, maximizing their quality of life and how much they tolerate rate control. What about rhythm control and or ablation? Then you call your friendly electrophysiologist who's probably not so happy about trying to ablate them because again, their hearts are so structurally abnormal and they're so old. So really it's a compromise to maximize their quality of life as best you can with rate and or rhythm control. But don't forget about the importance of anticoagulation. The left atrial appendage occluded device is a data free zone. No one quite knows a particular benefit in patients who have cardiac amyloidosis.

(12:07):

Another question that always comes up is, well wait a minute, what if they don't have atrial fibrillation? But you just think they're going to get it because their left atrium's so big. Should you just put them on anticoagulation prophylactically? Also a data free zone. But what about should you survey them? They have no symptoms of atrial fibrillation. Just check at a random point at a random time interval to four atrial fibrillation with an ambulatory ECG monitor. That's my practice. I'll do a 48-hour monitor once a year. Is that the right interval? Is that the right duration? I don't know, but I think it's so important to assess for this because it can change your management.

(12:45):

So that's atrial arrhythmias. Let's talk about devices. That's a tough one. What do you do when you have your patient with cardiac amyloidosis whose EF is 33%, who ostensibly otherwise qualify for defibrillator

for primary prevention of sudden cardiac death? That's a very tough question. One must also keep in mind that the guidelines do tell us that if your expected life expectancy is under a year, a defibrillator is relatively contraindicated because you're less likely to accrue a benefit, and at the mode of death in patients with cardiac amyloidosis is more often going to be a grade of cardiac PEA as opposed to a ventricular arrhythmia.

(13:21):

This comes down to a bit of shared decision making, and I have a different conversation with my 60-year old than with my 80-year-old when it comes to primary prevention. What about if they have an EF of 33% on a really wide left bundle? I do feel much more comfortable trying out CRT in that setting. I don't really know if it's going to work. Maybe their muscle is just so infiltrated with the amyloid, it won't help. But you know what? If it does and I can help them feel better, that is a worthy goal. So that's my sense of the atrial arrhythmias, the defibrillators and the CRT.

Dr. Robert Page (13:54):

Excellent. You answered that hard question amazingly. Thank you so much. So Dr. Ambardekar, you are the Director of Heart Transplantation at the University of Colorado. So I think this is a fair question to ask you. When do you consider advanced therapies such as the left ventricular assist device or cardiac transplantation? And also what are the specific challenges when you're facing advanced therapies in this population?

Dr. Amrut Ambardekar (14:26):

That is a great question and it is a very fair question to ask me. So if we're focusing on ATTR cardiomyopathy, the transthyretin cardiomyopathy, the first question I always try to ask myself is, does the patient actually need a heart transplant? Do we think their heart is sick enough to need a heart transplant? That's actually a question we ask for all comers that are referred to us for consideration of cardiac transplantation is do they actually need it? So there are some patients that we see that with modifications of their volume status and optimization of their diuretics, they can feel a little bit better with doing that. But otherwise, currently the treatments that we have for ATTR cardiomyopathy and the disease modifying treatments, while it is fabulous that we have treatments now and that we didn't before 2019, the treatments do not actually currently reverse the disease state.

(15:24):

So tafamidis is a ATTR stabilizer, as Dr. Kittleson mentioned, it stabilizes the transthyretin tetramer. It prevents any further dissociation of those fibers and any further deposition of those fibers within the heart. But it doesn't make anything better. So if you have a patient that you were very astute and made a diagnosis early in their disease course and they are New York Heart Association Class II and they have excellent functional status and they can still do all of their activities of daily living, they can still exercise, they're on minimal diuretics, that's a patient that you would expect is going to stay the same on our current treatments. And that is a patient you would expect would not need cardiac transplantation in.

(16:11):

On the flip side, if you have a patient that for whatever reason was diagnosed later in the game, and they have very significant symptoms, that's a patient that we think about cardiac transplantation. So some of the similar decision making characteristics that we look at for patients with heart failure, things like what is their functional status? What can they actually do? Sometimes we get objective measures of their functional status. We do what's called a six-minute walk where we have people just measure how far they can walk in six minutes and if they can't get more than 150 meters in six minutes, that's

concerning. The simple way I think about that is the track that goes around the football field at your high school, that is 400 meters around. If you can't make it even halfway around that in six minutes, that means you're pretty limited. Sometimes we do the gold standard, which is the peak VO2, so a peak VO2 that's less than 14, that's concerning or less than 50% have predicted for your age and gender, that's concerning and that would suggest poor functional status.

(17:08):

Other clues are frequent hospitalizations. Need for inotropes, high diuretic doses, those would be all, or cardiorenal syndrome, someone who has elevations in their creatinine as you're trying to titrate their diuretics. So those would all be red flags to me to think the heart might be sick enough to think about cardiac transplantation. The second part of your question was what are the challenges? And there are many challenges. So I'd like to simplistically think of that is the rest of the body good enough to handle a cardiac transplant? A heart transplant's a major surgery and we can't do a heart transplant without the rest of the body being able to handle such a big surgery. And so in ATTR cardiomyopathy, frailty is a huge factor. I think we have gotten away from using strict age cutoffs, but look at more physiologic age and the way we assess physiologic age is frailty assessments.

(18:05):

So there's a number of frailty assessments that are out there that are validated. Oftentimes working closely with physical therapists and occupational therapists as part of the transplant evaluation process to get a sense for is a patient that may be older, are they strong enough or not frail that they could handle a surgery? Looking at comorbid conditions is also important. For patients that have coexistent neuropathy, it's critical to work with a neurologist to make sure that their amyloid polyneuropathy, if they have it, is controlled and not at a stage where it would affect outcomes after cardiac transplant. Looking at other factors such as do they have concomitant, comorbid, renal disease, liver disease? Those are all things that play into whether they would be a candidate for a cardiac transplant.

Dr. Robert Page (18:49):

Awesome. Thank you so much. These are excellent, excellent perspectives. So thank you Dr. Ambardekar. So Dr. Kittleson, you know Dr. Ambardekar alluded to this as well, but two parts of this question. Number one, who is not a good candidate for pharmacotherapy? And then secondly, how do you measure the success of the treatment? We've already highlighted there that in terms of mortality, it's meh, but what do you do in your practice and when do you consider changing therapies? That's a loaded question. Sorry about that.

Dr. Michelle Kittleson (19:25):

No, no. Dr. Page, I like this one better. Thank you so much. Okay, so let's start with who do you say no to? Because really one of the cardinal qualities of an outstanding clinician is knowing when to say no. When? Because you don't just want to give someone something. You want to give them something that's actually help them feel better and live longer. So the patients, you don't want to give the one FDA-approved evidence-based therapy, tafamidis for transthyretin cardiac amyloidosis. There's two. Maybe there are two, wow, they're an asymptomatic gene carrier. They got their 23andMe, now they know about it, they're 30 years old. Their echo is perfect. We don't know. That's a data free zone. You're not going to give them prophylactic tafamidis.

(20:11):

Second group, what if they're too sick? So if you look really interestingly into the subgroup analyses of the ATTR-ACT trial, you see that the less sick you are, the more you benefit. And that makes sense. It

doesn't reverse disease, it prevents progression. The earlier you start, the better you're going to do. So if you have someone who is NYHA Class IV who is a symptomatic with dressing and showering or even at rest, was multiple hospitalizations with severely low blood pressure, really worsening kidney function, the patient, Dr. Ambardekar told us about that you might think about a transplant, but you know what? They're so old you can't do that either. That's not the person who's going to benefit from Tafamidis. The horse is out of the barn. Those are the people for whom I counsel them that our best approach might be a goals of care, quality of life discussion, as opposed to a medication that's really not going to help them. And they're also patients who advance to that stage who I often discontinue and I say, "Why are we wasting the resources on a therapy that's not going to benefit you?"

(21:11):

So that's your first question. The second question you asked was regarding how do you monitor the success of these therapies? I love that question because we are really living in the wild, wild west of cardiac amyloidosis. There's so much we don't know. Really, we have one therapy and you start it in the right person that is symptomatic transthyretin, cardiac amyloid doses, not too advanced, hopefully, so they'll actually accrue some benefit to Tafamidis. However, how do I know it's working or not working? Well, we don't check follow-up scans. You don't technically even need a follow-up echo. You don't gauge it by the wall thickness. When patients come to me and say, "How am I going to know if it's working?" I say, "Let's ask the counter to that question, which is, what are we going to do if we had a test to show us it wasn't working? There's nothing else to be done."

(22:05):

There's one therapy and we give it. I can imagine a time in the future where we have ways to gauge response and or tailor therapy to a different phenotype, but that's not where we are right now. So you tell patients this medicine won't make you feel necessarily better, but it will prevent you from feeling worse. And the natural history of this disease feels a lot like just getting old. So congratulations, you got a disease you were lucky enough to get because you got old and you're going to feel like you're getting old. But we can try to slow down that process somewhat with this medication.

Dr. Robert Page (22:36):

Excellent. Thank you. Thank you. Now, as the pharmacist myself, I realize these are highly expensive medications and my other hat that I wear in terms of managing, helping manage our Medicaid benefit here in the state, very expensive medication. I know cost is one big barrier. I guess my question to both of you is can you, and we'll start with you, Dr. Ambardekar, can you comment number one, has cost been your biggest barrier? And then also number two, are there any other, you both have been done an excellent job with talking about some barriers, but are there other barriers that you've run into when trying to prescribe these therapies and how have you dealt with them? So we'll start first with you, Dr. Ambardekar.

Dr. Amrut Ambardekar (23:25):

Thank you. So I think we use our pharmacists quite a bit and we rely on our pharmacist. So the cost is a definite concern. There's a sticker shock and almost a stress that patients and their family members have at the sticker prices of all of these amyloid disease specific treatments. There is a lot of hoops to jump through in terms of prior authorization paperwork and dotting your I's and crossing your T's, and having a team of nurses and pharmacists and medication access specialists to help navigate those costs is critical. And thankfully at University of Colorado, a lot of other centers, we have a team in place to help patients and their family members and clinicians navigate those things.

(24:10):

There's also a lot changing with the cost of these medications. Tafamidis for ATTR cardiomyopathy, most of the patient with wild type ATTR cardiomyopathy are on Medicare. And Medicare, out-of-pocket drug costs are the subject of national discussion, which is too much to go into in the course of a podcast like this. But I think there's potential to be a lot of changes. And what are the out-of-pocket maximums for Medicare out-of-pocket costs for drugs in the future? And so the short answer is we use our pharmacist and cost is a major issue. And navigating those costs and the financial aspects of these medications is critical in the care of these patients.

Dr. Robert Page (24:52):

Excellent. How about you, Dr. Kittleson? What is your experience been?

Dr. Michelle Kittleson (24:57):

So I don't think I could add much to what Dr. Ambardekar has already eloquently outlined is the challenges we face. But I'll just bring up two points that I think are very poignant for me. Number one, let's all be honest here, a chronic amyloidosis is not rocket science. It's actually not that hard to diagnose and it's not that hard to treat. So it pains me philosophically, ethically, morally that there are these patients who come and see me, your general cardiologist couldn't diagnose it or put on a prescription because it's not that hard. But because of the in paperwork, the resource utilization involving getting the prescription made, we have a dedicated nurse in our office whose only job is to deal with tafamidis prescriptions. It should not be like that. And that then leads to other layers of inequity and disparities in accessing appropriate care. So I know everything about medicine. I know nothing about policy, but those two issues I find incredibly challenging and I wish our patients didn't have to deal with.

Dr. Robert Page (25:55):

No, I completely agree. It's interesting, I've talked to people around the country about this and it's interesting, if you're in a Medicaid expansion state, it's actually really ease to get the drug compared to third party, part D. Lots of, yeah, I completely agree. So as I said, I want to thank you both for this excellent discussion. So I'm going to wrap things up and I'm going to start with you Dr. Ambardekar. What are your three take home points?

Dr. Amrut Ambardekar (26:24):

First of all, cardiac amyloidosis is not rare. People think of it as a zebra, but if you look for it, if you're a practicing clinician that takes care of patients with heart failure, atrial fibrillation, you have an amyloid patient in your practice, you just have to look for it.

(26:40):

The second thing that we didn't go over but is poignant is that it is actually not that hard to make a diagnosis of amyloid. You don't need to refer somebody for a cardiac biopsy or something invasive. And most patients, if you follow diagnostic algorithms that have been published and are pretty easy to follow, the American Heart Association statement that Dr. Kittleson led from a few years ago is a great example, but you can make a non-invasive diagnosis of amyloid in the majority of cases.

(27:08):

And the third is that amyloid is treatable. And I think that's huge. I would agree with what Dr. Kittleson said. When I was in medical school, there wasn't a lot we could do for these patients, and things have really changed.

Dr. Robert Page (27:19):

Excellent. How about you, Dr. Kittleson? What are your three take home points?

Dr. Michelle Kittleson (27:24):

I have the exact same three as Dr. Ambardekar Three more. Okay. Challenge accepted.. Number one, don't forget tafamidis is the only FDA-approved defective therapy for transthyretin cardiac amyloidosis. The earlier you start it, the better your patients will do.

(27:40):

Number two, if they have atrial fibrillation, you anticoagulate them regardless of their CHADS2-VASc score.

(27:46):

Number three, you must reassure patients and empower them that, "Listen, I can't tell if it's working or not. You're going to get older, you're going to feel worse. But let's do everything in our power to help you feel as good as possible for as long as possible." That really is the story of cardiac amyloidosis.

Dr. Robert Page (28:02):

Perfect. This has been absolutely wonderful, and I know both of you are extremely busy, but we are so fortunate today to have both thought leaders in the field summarizing with regards to the forefront of pharmacotherapy. And again, I want to personally thank you, the AHA for your expertise and your time and dedication within this field.

(28:25):

So again, I do want to highlight that this activity is being supported by an independent medical education grant by Pfizer. The views and opinions in this activity are those of the speakers and reflect the synthesis of the science. Content should not be considered as the official policy of the AHA. And if you want any additional information, please visit learn.heart.org. Let me repeat that again. learn.heart.org for more education. Again, I really want to thank our excellent speakers today. Thank you so much for your time and energy and this excellent discussion. And thank you today for listening in on this excellent podcast. And I hope you have a great day.