Dr. Palmer: Hi everyone. Welcome to the American Heart Association, ATTR, closing the knowledge gaps in transthyretin cardiomyopathy. This is a podcast series that we're having with the American Heart Association today. And I'm Dr. Renee Bullock Palmer, an attending cardiologist, and the director of Non-Invasive Cardiac Imaging, as well as
[00:00:30] the Director of the Women's Heart Center at the Deborah Heart and Lung Center in New Jersey. The series have intended to increase the ability of healthcare practitioners to recognize and provide early identification of patients with transthyretin amyloid cardiomyopathy, commonly referred to as ATTR-CM, and to ensure that accurate diagnosis and timely initiation of the proper treatment therapies is being done before the onset of cardiac dysfunction. Being able to make the correct
[00:01:00] diagnosis of ATTR and devise a treatment plan is grounded in the understanding, that this life-threatening pathophysiology of cardiac amyloidosis and engaging in to evaluate the strategies for early detection.

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[00:01:30] education. In today's podcast, we will be discussing the areas of uncertainty and future directions in the diagnosis, prognostic assessment and management of ATTR cardiac amyloidosis. Before we begin, we will review the learning objectives for this specific podcast. So at the end of this podcast, all attendees should be able to outline the current gaps in knowledge about effective screening tools for ATTR cardiac amyloidosis, and they should be able to understand the limitations and need for future investigation in determining the best diagnostic tools to follow disease progression of ATTR cardiac amyloidosis.

[00:02:00] And finally, they should be able to outline the current gaps in improving access to effective therapies of ATTR cardiac amyloidosis in all patient populations regardless of race, ethnicity, gender, or socioeconomic status. So today we're joined by our distinguished colleagues, Dr. Martha Grogan and Dr. Justin Grodin. And Dr. Grogan, why don't we start with you introducing yourself.

Dr. Grogan: Thank you so much for having me, this really exciting podcast. I'm a non-invasive
[00:02:30] cardiologist at Mayo Clinic in Rochester, Minnesota, and I'm the founder and director of the Cardiac Amyloid Clinic here.

Dr. Palmer: And Dr. Grodin?

Dr. Grodin: Yeah, I want to echo Dr. Grogan's sentiments. This is certainly a delight to be invited and it's really a pleasure to be amongst all of you in discussing these really fun and interesting and important topics. I'm an advanced heart failure and transplant cardiologist at UT Southwestern. I co-direct our multidisciplinary cardiac amyloidosis
[00:03:00] program and my area of research interest is understanding the natural history of ATTR amyloidosis.

Dr. Palmer: Great. Thank you both and welcome. So Martha, my first question goes to you. Should we screen for ATTR cardiac amyloidosis? And if so, in which populations? And then which diagnostic test would you recommend for screening?

Dr. Grogan: That's just a fantastic question and I think I'll back up just a little bit. It depends on our definition of screening. So certainly high risk to highlight would be patients with unexplained heart failure, unexplained atrial arrhythmias or conduction system
[00:03:30] disease, especially those who have a history of bilateral carpal tunnel syndrome, spinal stenosis, biceps, tendon rupture some of these other orthopedic manifestations. And also in Black Americans because of the increased prevalence of hereditary ATTR cardiomyopathy. So those are patients that where clinically, we're going to be looking for those patients. I think the idea of screening though, is more
[00:04:00] applicable to hereditary carriers. We don't really know how soon we should screen. We often do some very basic baseline testing, which might include cardiac biomarkers, an EKG, and in some patients, an ECHO and a PYP scan, depending a little bit on the age of the patient.

This is all still pretty unclear. We do have emerging tools such as things like artificial intelligence. We have an algorithm applied to the ECG. One thing I think that we
[00:04:30] might want to be cautious about, are patients who have had carpal tunnel release, for example. And we've had a lot of enthusiasm, should we be staining all these specimens? But most patients are negative at the time that they have the carpal tunnel release and it creates a true Pandora's box, a lot of anxiety, potentially unnecessary testing. So certainly if they have bilateral carpal tunnel syndrome and heart failure at the same time, then we should consider staining the tissue and looking for cardiac involvement. But I think we really need to think about things like
[00:05:00] bilateral carpal tunnel and spinal stenosis more as a cardiovascular risk factor. And I don't think we should do widespread screening at this time, just as we don't have every diabetic go to the cath lab.

Dr. Palmer: Great. So you mentioned biomarkers. So are there any specific biomarkers that you use as screening? You want to speak a little bit more on that?

Dr. Grogan: Sure. So NT-proBNP or BNP and troponin are probably the most sensitive, but still
[00:05:30] they're certainly not diagnostic. If they're completely normal, it's pretty unlikely that the patient has cardiac amyloidosis. So I think in a high risk group like a carrier, that can be a very reassuring finding. But that's not something ready for widespread screening of patients, at least in my opinion. I'd be interested in what Justin thinks on that.

Dr. Palmer: Justin?

Dr. Grodin: As Martha knows, my thing is biomarkers, especially in this population, and I would
[00:06:00] agree with her. We know that those biomarkers are elevated commonly in individuals that have cardiac amyloidosis and it's undiagnosed, and that increases our pre-test probability for more dedicated testing. But I think when we're talking about carriers and we're talking about people that might be genetically predisposed to developing hereditary ATTR, we know from epidemiologic studies, so population-based studies

that trajectories of biomarkers are different in comparison with non-carriers over time.

[00:06:30] But those differences we detect on average over populations, whereas when you're at the patient's bedside, they really might not be readily clinically apparent. We have some other things that I would agree with Martha, are really not ready for prime time. Things like looking at prealbumin retinol-binding protein 4, there's some more experimental biomarkers that people are developing but really haven't been tested in large populations. And some of these are involved with looking at, they call it non-
[00:07:00] native TTR or amyloid intermediates. In other words, these TTR species that are on their way to becoming amyloidosis. But none of these have really been validated as screening tools, although they are interesting and promising.

Dr. Palmer: Right. So Justin we'll stay on your topic of screening a little bit. So how does bone scintigraphy perform as a screening test? And if so, in which populations, do which we look at those with the lower penetrance of the disease compared to specialized amyloid centers, where they may have a higher prevalence of disease. And finally,
[00:07:30] how should asymptomatic allele carriers of TTR mutations be followed for disease penetrance?

Dr. Grodin: Well, Renee, those are three terrific questions that we could probably, I'm sure Martha and I could spend all afternoon debating each one of them. The first one that I will tackle really is PYP. And I think one thing we all have to recognize is that PYP scanning is, the test characteristics are validated in individuals that have manifest ATTR where, Martha and I are probably not going to debate if this person has amyloidosis.

[00:08:00] It's just really more of finding out what type this person has, and that's really the utility. There are some data out there that do suggest that carriers might have low level uptake, but there's one small study that comes to mind from Boston, but it's really unclear as to whether these tests were protocolized, if they had SPECT imaging as opposed to planar imaging. So it's really an area of uncertainty. I think what's nice
[00:08:30] about PYP is that if it's positive and it's a true positive with a good test, you know that that person in, within a reasonable level of likelihood, has the disease. But I think what it doesn't tell us, is whether there's a little amyloid there or really what is that natural history and whether we're capturing it, we don't know at what point a PYP becomes positive based on the amyloid burden that's deposited in the myocardium.

Dr. Palmer: Great. And Martha, do you have anything to add to that?

Dr. Grogan: Yeah, the only thing to add is again, screening. We do need to be cautious, especially
[00:09:00] if we start applying this to less differentiated populations. So just a reminder to the audience, that the use of nuclear cardiac scintigraphy, PYP, DPD, the consensus statement requires that the patient have actually heart failure with a typical echocardiogram or cardiac MRI, the patients that were in that landmark study were relatively advanced and there was a high prevalence of disease. So when we apply
[00:09:30] this to lesser chance, when the pretest probability is lower, you are going to have a

much lower positive predictive value. But I'm very nervous if I don't have a pretty characteristic ECHO or MRI, they don't always have to have full-blown heart failure.

But I think that's been lost a little bit. So we see patients kind of indiscriminately getting a PYP scan and there really aren't those other factors. I'm very cautious in that case. Lastly, it's for people to remember there are other causes of positive PYP.

[00:10:00] Number one is myocardial infarction. So patient comes into the hospital with heart failure, PYP positive truly could be, an acute MI. So that's something to remember, there's a few other causes, but that's the only other caution with screening. I feel much more comfortable when it's a carrier because then I think we really can probably detect early disease and maybe you see some subtle changes on ECHO or biomarkers too.

Dr. Palmer: Right. So Martha, staying with you, for patients who have been diagnosed now with the disease, what's the best combination of prognostic variables for ATTR and which

[00:10:30] biomarkers, if any, are more effective for following these patients?

Dr. Grogan: The nice thing is that cardiac biomarkers are really powerful. And if you look at the explosion of literature in cardiac amyloidosis, everyone wants to say something that's prognostic when you should always read the literature and say, well, was it independently predictive of biomarkers? So I'm happy to say the first staging system was our staging system for wild-type TTR amyloidosis, which uses NT-proBNP and

[00:11:00] high sensitivity troponin. And then the UK, the National Amyloidosis Center, published a very similar staging system.

They used NT-proBNP, the same cutoff of 3000 and the estimated GFR by creatinine. So they're really very similar. So if you have creatinine, NT-proBNP, or even you can use BNP and troponin, you have a good prognostic staging system. Recognize though that the data from that, was before any treatment. So if you're counseling a patient,

[00:11:30] some of the patients have read these articles and they know that the median survival is about three and a half years if you're an intermediate stage or of even all comers, but that's in the era before treatment. So they're very powerful staging systems. And you can throw in other things from ECHO and CMR, but really the biomarkers tell you most of what you need to know.

Dr. Palmer: And Justin, just want to get your opinion on that. And what's the role of imaging for prognostication?

Dr. Grodin: I agree with Martha. I'm a little bit more biased to biomarkers, but I think one thing to

[00:12:00] emphasize is their simplicity and ease of measurement. I mean, these truly can be democratized throughout as opposed to, imaging and some other tests that, there might be differences in expertise in the way these things are interpreted and even protocols. I think that really underscores the importance of the work that Martha and her colleagues have done. And then our colleagues in the UK at the NAC.

That being said about imaging, I mean, you could pick a number of imaging metrics, LV wall thickness, diastolic function, systolic function, EF, you can pick MRI metrics,

[00:12:30] intensity of uptake on PYP scan, and you could probably find a paper that is going to

show you that these things are prognostically informative. And for me, I think largely they're used for diagnosis and we can look at them independently. And it might be interesting to pull a paper that says that this could be clinically relevant, but I agree with Martha. At the end of the day, a lot of these point estimates for survival are really reflective of the untreated natural history. And now we're in an era where the
[00:13:00] natural history is modifiable with a lot of these targeted treatments.

Dr. Palmer: So staying on the topic of treatments, so once you have started treatment for these patients, how should one measure disease progression and are there various domains such as quality of life, functional measures, biomarkers, imaging that may show progression? Is there an easier marker that we can use for disease progression?

Dr. Grodin: This is a major area of uncertainty, and I can tell you at the end of the day, it comes
[00:13:30] down to how are patients feeling and how are they doing. For patients with cardiac ATTR and heart failure, how well compensated they are, how stable is that? Are they staying out of the hospital? But then we can also break it down even further. Some of the biomarkers that Martha had mentioned may be useful such as NT-proBNP or troponin, are these going up? Are these going down? Again, but those might be related to other factors that aren't related to their amyloid. We can have concomitant
[00:14:00] chronic kidney disease. There are a number of questionnaires that can assess an individual's degree of dysautonomia or autonomic dysfunction like the COMPASS 31 or the Norfolk diabetic neuropathy questionnaire, which is validated in patients with ATTR and polyneuropathy. There's some centers around the country that assess these regularly to determine the progression of some of these entities.

And then there are things that are even more simple, like looking at their albumin adjusted weight, which is kind of a marker of healthy body weight as opposed to a edematous body weight. Metrics of nutrition, and then it's probably different for
[00:14:30] different individuals. When we're looking at an 80-year old with wild-type ATTR, some of the metrics of disease progression might be different where we're focusing on self-efficacy, mood, nutrition, frailty, very different than let's say somebody who's in their fifties that might have hereditary ATTR and polyneuropathy and heart failure. Some of the way that we would assess their disease metrics might be more, perhaps ATTR specific or might even be more disease focused.

[00:15:00]
Dr. Palmer: So Martha, staying on a topic of disease progression, are there biological processes such as TTR stability, TTR kinetics or TTR ligands that can be used to monitor progression? And then can we use disease progression to tailor therapy in terms of which drugs do we use and when do we decide to switch to a different drug?

Dr. Grogan: Right now, we do not have simple tests to monitor the efficacy of these drugs. We use indirect measures. So for example, prealbumin is transthyretin and if a patient's on a
[00:15:30] stabilizer, normally it should go up and that's a sign that the stabilizer's working. If they're on a silencer, it's important to recognize that it should go down, it should be very low, and sometimes people get confused about that. So that gives us an idea if the drug is working, but that doesn't necessarily tell us what the patient's outcome will be. So similar to what Justin said, I tried to explain to patients that, eventually we

probably will have other tests clinically available of TTR stability and things like that to help us with those issues. But for right now, we follow the patient mostly clinically.

[00:16:00] How are they feeling? What's the dose of diuretic?

Are they in the hospital? Simple biomarkers and a six-minute walk or something like that. A lot of imaging right now does not change therapy because currently, we only have tafamidis approved for cardiac involvement specifically. And for wild-type patients, that's the only approved therapy. Hereditary patients may be on a silencer, but we don't have data showing us that we should have patients on two drugs or

[00:16:30] there's no dose adjustment. So I think it's an important area of investigation, but clinically, I try to minimize doing additional tests if they're not going to change therapy.

And I try to set the stage with the patient upfront, that these tests that we did are great for diagnostic purposes, but things such as following your wall thickness on ECHO, that is not at all going to tell me if you're getting better or worse or even if the drug is working, it's because it's so variable. So I don't do a lot of follow up imaging

[00:17:00] unless there's a specific reason. So for example, aortic stenosis that might need intervention on or pericardial effusion probably as far as imaging techniques that we do have, CMR probably has the most potential and eventually we'll get there with our research studies, but clinically it's really very simple monitoring.

Dr. Palmer: Great. So Justin, before we pivot, anything to add to that?

Dr. Grodin: I agree 100% with Martha. I mean, I think she's highlighted some very elegant tests that we have, but their utility's uncertain. And then we also really don't know what

[00:17:30] some of these tests are actually representing when we check them because we know in a treated patient, is something about the disease more quiescent, even though the heart might look similar than in an untreated patient. I'll just make a brief comment about some of these other tests that you mentioned. Assessing TTR kinetic stability, looking at some of these pre or amyloidogenic abnormal aggregates that could be on

[00:18:00] this amyloidogenic cascade. These things are really not ready for widespread use. These are largely subject to research laboratories, highly specialized and at least haven't been at the point where we can scale a lot of these assessments. So right now they're largely within the realm of research, although they're promising. But again, the main issue is scalability.

Dr. Palmer: I'm going to pivot now to regression. Can TTR amyloidosis be reversed and if so, what factors predict regression of the disease? Justin, that's for you.

[00:18:30]

Dr. Grodin: I get asked all the time, probably on a weekly basis, when we have that discussion that a patient has amyloidosis and then which naturally translates to treatment. And then what is my long-term outcome? And at this point, one thing that I will say before I speculate is that, we don't have solid evidence that the treatments do reverse the disease. We do have evidence that supports that the disease is stabilized. We think it might be halted, it might be slowed. It's kind of unclear. We know from some

[00:19:00] subgroup analyses from clinical trials that patient symptoms and even the cardiac

phenotype might stabilize over time in comparison with people that were treated with placebo in those studies. And then I'll speculate, well maybe again, we don't know if the heart somehow adapts to the fibrils that are deposited. Is there some healing that is going on? It's really unclear.

And then to what degree are circulating fibrils toxic themselves to cardiac function? And that's an unknown. We suspect that might be the case and that might even be
[00:19:30] different for people with different TTR genotypes. And then the last thing I will say is, this is quite a hot topic because just a few weeks ago there was a report by the NAC at the UK where individuals did develop antibodies to ATTR. And at least this tells us, or at least for those individuals, their cardiac function did appear to improve or the way that amyloid was measured appeared to improve. Now, those data haven't really
[00:20:00] been replicated. It'd be nice to see that in other individuals and definitely to learn more. And then there are companies that are developing treatments that might help with regression and they've shown promising early phase one studies, but at this point these are still areas of uncertainty, but that really is the holy grail.

Dr. Palmer: I'm going to be discussing here the diverse treatment medications that we have on the market or have available in research and stuff. How do the efficacy of stabilizers
[00:20:30] and silences compare? And do TTR stabilize for different efficacy and side effects of profile?

Dr. Grogan: So that's a fantastic question. We are probably never going to have a head-to-head comparison of stabilizers and silencers due to the history of how the trials evolved. So we do not know if one is superior to another. I think what we are seeing, and we're going to have more results coming out, is both treatments are effective in slowing
[00:21:00] progression. Perhaps over time patients do stabilize and eventually I think we will start to see some regression. The key thing to remember is that TTR amyloid is a really slowly progressive disease. Think of a hereditary patient. They've had that abnormal TTR their whole life. So we need to realize that probably we need longer follow up. Sometimes for clinical trials, there's a push to, oh, we want to know what happens at 12 months. Well, most of the time that's not going to be anything that exciting.

So it's a slowly progressive disease. So improvement takes time. And so we do not
[00:21:30] know how they compare. Over time, we'll have more data. I hope maybe we have some registries or things to help guide us. The stabilizers, as far as the stabilizers in our experience, we don't know of differences in efficacy personally with the patients I've had on clinical trials now with both of the available stabilizers and actually also patients that are treated with Diflunisal, the main difference is we do use diflunisal as a stabilizer in some patients. So that obviously has more potential side effects. But
[00:22:00] with the other tafamidis and acoramidis, we don't know of a true difference. They're very well tolerated in those two medications. I think you mentioned the combination of therapy. This is also uncharted territory. Now some patients end up on combination therapy because of historical, they were in a clinical trial on a silencer and then Tafamidis became approved and they got on that.

And especially if you have a hereditary patient with a very malignant family history,
[00:22:30] you want to pull out all the stops. But should patients really be on dual therapy and if

they're on a silencer, that markedly reduces transthyretin, should we really be spending now it's about $250,000 a year to stabilize a little bit of TTR that's left? So those are really unanswered questions. As we get more therapies, we know that it's possible that we'll have a silencer approved for wild-type TTR perhaps within the year. What the labeling will say, I have no idea even knowing the data quite well, how
[00:23:00] we will use it, I don't know. But the last thing I would emphasize is that, if you treat patients early and you stabilize them, then I feel quite confident that we are changing the natural history of disease. And over time, not only do they become stable, but they probably will actually improve.

Dr. Palmer: And do you have any specific order in which you choose a therapy, so do you start the stabilizer first or silencer first?

Dr. Grogan: For right now, that's only an option in a hereditary patient. So if a hereditary patient
[00:23:30] has neuropathy and cardiac involvement, in theory, we could prescribe more than one drug. I personally don't usually do that. Again, sometimes a hereditary patient, sometimes they've even had liver transplant and then they end up on two of these therapies. If they're not doing well on one, yes, we do add another one. But for your average patient right now, they're either going to qualify for a silencer or stabilizer. Again, a hereditary patient could qualify for both if they have neuropathy and cardiac involvement. I don't very commonly sequence the drugs because it's not usually an
[00:24:00] opportunity that we have.

Dr. Palmer: Justin, do you have anything to add to that?

Dr. Grodin: No, I agree completely with Martha. And I think one thing that I want to emphasize that she mentioned is really the cost of these treatments. In particular from a biological standpoint, if I have a patient that's on a silencer, and at least with clinical assays, we really can't measure their prealbumin or their TTR. To me, it's a little bit uncertain as to the benefit of TTR stabilization for individuals like that. And so I have a
[00:24:30] hard time justifying a drug that might cost a quarter of a million dollars when they're already on a drug that is quite expensive. And then one thing we at least will hopefully find out with some clinical trials that are currently enrolling. So for example, there's the CARDIO-TTRansform trial. This is among others where they're allowing concomitant usage of Tafamidis and study drug. And then we'll see from subgroup analyses whether there was an additive benefit, whether it was a wash.

[00:25:00] And so time will tell and we'll probably have those results in a few years. But what we won't know is true comparative effectiveness. That is going to give the answer to the people that what they want to know is, which drug is better. And then another nuance is that we hope there'll be another stabilizer available towards the end of the year or maybe beginning of 2024. Even clinical trials themselves and the populations in which these therapies are being studied are different. So it's not apples to apples, it can be apples to oranges. So just highlighting some of the challenges and really trying
[00:25:30] to figure out what is the best drug among our choices.

Dr. Palmer: Right, so Justin, staying in your corner with heart failure, what is the role of defibrillators and pacemakers in patients with ATTR? And when should patients with

this disease be considered for advanced surgical heart failure therapies if there's such a role such as LVAD and cardiac transplant?

Dr. Grodin: [00:26:00] Well, those are great questions, and I can tell you right now it least for ATTR, we really follow the guidelines for just about anybody when it comes to placing a defibrillator or a pacemaker, whether it's pretty clear if somebody's had sudden death, they've had VF or they've had sustained VT, that those individuals would merit consideration for a secondary prevention ICD, then I think it becomes a little bit uncertain when we try to apply information from perhaps more common or more conventional cardiomyopathies with low EF for primary prevention ICD, the benefits are uncertain, but we do extrapolate those data. But a lot of the criteria, adjusting [00:26:30] heart failure medications and ejection fractions, sometimes those medications are not well tolerated in this group because they can cause lower blood pressures or worsening symptoms. And then the ejection fraction might mean something a little bit different in patients with amyloid because their hearts really aren't big and baggy, they're thick and stiff.

And then pacing, we typically look at the classic indications in particular if they've got substantial evidence of high grade AV block, et cetera, or sick sinus syndrome and some more traditional indications. And then when it comes to LVAD and transplant, [00:27:00] I'll talk about LVAD first. And LVADs were largely designed, at least the continuous flow devices that we have, were designed to unload ventricles that really are big and baggy. So dilated left ventricles, and they work best in individuals that don't have substantial right heart failure or RV failure. Now for patients with amyloidosis, they really don't have either or ATTR, their ventricles are thick and stiff and the chamber [00:27:30] sizes are smaller. So the practicality of trying to fit an LVAD cannula in one of those chambers is not so straightforward. And then a lot of our amyloid patients have substantial right heart symptoms.

And so whether this translates to some predisposition and risk of RV failure is unknown. And I can tell you with Intermacs data, there was a paper that we published a few years ago. There were only, until about 2017 in the history of Intermacs, which captures all the durable mechanical circulatory support devices in North America. So [00:28:00] the United States and Canada, there were only about 46 individuals implanted with durable MCS. And just over half of those, were in LVADs. And in comparison with other restrictive cardiomyopathies and the more conventional dilated cardiomyopathies, they were associated with a greater risk of death even when transplant was an option. We don't know what type of amyloid those individuals had, it wasn't captured. But I think what it tells us is that if we consider an LVAD for these [00:28:30] individuals, we need to be really cautious and we need to have really good data at a high level of expertise to make sure it is the right thing for that patient.

And then the last thing about transplant, at least for ATTR. So for ATTR where there's mostly cardiac involvement and there's not much extra cardiac involvement, in other words, there are non-cardiac comorbidities that will influence how somebody does with transplant. Transplant can be a great tool for people with really advanced [00:29:00] disease. For individuals that have a lot of non-cardiac ATTR symptoms, we see this more commonly in some of the variants that might have predominant nerve

involvement. If there is anything that would influence how well they do post-transplant, so like a lot of autonomic dysfunction, gut dysmotility. So things of that nature that necessarily wouldn't be treated might influence whether or not we proceed. And then now we're at least a little bit more liberal about offering transplants to ATTR patients because it's pretty clear they do quite well when well
[00:29:30] selected. And then now we have treatments. Now the efficacy of those treatments post-transplant is an area of uncertainty, but for individuals where we can secure those therapies, it at least is a nice option in the modern age.

Dr. Palmer: You touched on the transplant. If you transplanted these patients, would it be reasonable to also keep them on that stabilizer to prevent any deposits of amyloid in the transplanted heart?

Dr. Grodin: We are currently enrolling for a clinical trial that's sponsored by Pfizer that is testing the safety and efficacy of tafamidis in individuals that were transplanted for ATTR. So
[00:30:00] we really don't know, but we do at least suspect these treatments are beneficial. Our own practices are if they've got hereditary ATTR neuropathy and then they get a heart transplant and they were on a silencer before, we keep them on their silencers after, because we have to recognize that there can be non-cardiac manifestations that progress despite addressing their severely limited organ. And then for the stabilizers, we do prescribe them for individuals that have payers just practically that
[00:30:30] aren't really a financial burden to these individuals. But as far as the long-term outlook and the efficacy, it's a little bit uncertain for those individuals.

Dr. Palmer: So before we move on to the last two topics, Martha, anything to add to that?

Dr. Grogan: We saw that in a group of wild-type TTR patients who had undergone heart transplant, traditionally it had been thought that wild-type patients have predominantly a cardiac phenotype. But the patients we had, I think it was six out of
[00:31:00] nine, within five or six years, developed peripheral and or autonomic neuropathy. And the concept is that for whatever reason, these patients historically mostly have cardiac dysfunction and they die before they manifest the peripheral neuropathy. And some of these are very severe neuropathies. So I think just keeping an open mind. So in our case, if a patient has had a heart transplant, we try to have them on therapy
[00:31:30] either continuing what they were on and actually if they do not have access to either a silencer or to Tafamidis, we have cautiously used diflunisal in that situation too because they have a new heart.

It's all about what their renal function is. But we think that it's probably a good idea based on our clinical experience. We already knew that from hereditary patients that liver transplant alone certainly wasn't a cure. So that's the way we approach it. But I think that's also having an open mind about this disease. There's a famous diagram
[00:32:00] from our late colleague, Dr. Rapezzi of TTR mutation. It's a fan that shows these are the ones that cause neurologic disease, these cause cardiac disease, and the ones in the middle have an overlap. But as we see more patients, hereditary patients, the vast majority have an overlap if you look closely enough. And again, patients who might have mostly cardiac disease, if you keep them alive long enough, they are going

to have other systemic manifestations. So I think to give someone an organ transplant and not being treated the underlying problem, we're really not helping anyone then.

[00:32:30]

Dr. Palmer: So we already spoke about some advanced treatments, advanced testing, how can we improve access to care for TTR cardiomyopathy in underserved populations and patients who are of lower socioeconomic status? So Martha, my questions for you.

Dr. Grogan: That's so important because we know that we have high risk groups within our country that are under-recognized. So especially individuals who are Black or of

[00:33:00] Caribbean descent are often felt to have hypertensive heart disease when they indeed have cardiac amyloidosis. Raising awareness within the provider community is very important, but I think we really need to get to the community itself, whether that's through the barbershop or churches or community centers to let patients know of this risk. And of course, there'll be wild-type patients too, and hereditary and in lower socioeconomic groups in general, they just don't have the access to healthcare.

[00:33:30] Things that might help us are things such as point of care ultrasound. In our case, we're very excited about the AI ECG because you can do it with a mobile device. It scares me to say in a way you could do it with Apple Watch because I don't know how many people, but you could envision being in a clinic where you had these simple tools that have high negative predictive value.

So if you're worried about an at-risk person, is it really hypertension causing the heart failure or is it amyloidosis? Simple tests that we could do in the office for people that

[00:34:00] are not going to be able to come back for frequent follow-up visits or are not going to necessarily have access to MRI and other techniques. But we have a lot of work to do in this area. The other key thing obviously is the cost of the medications. Although patients who are really limited in their income usually will not pay for their medications, but how do they even get to the point where they get the diagnosis is more important?

Dr. Palmer: Right. So Justin, this is the final question, but just, if you could add to that and for

[00:34:30] your question, how does the cost of therapy influence adherent treatment and outcomes? And do you think the cost of these treatments will affect the development of novel therapies in the research pipeline, Justin?

Dr. Grodin: Oh, well, there's no question, and I'm sure I'd be interested to hear what Martha says, but there's no question that the cost of these therapies influences their utility. And we see all variations in Medicaid, Medicare, what gets covered, what copays are, out-

[00:35:00] of-pocket costs are for individuals with private insurance, PPOs, HMOs. And then sometimes, some of the companies will have patient support programs where probably through grant funds where they can get the cost of these medicines cheaper. And so I think that really influences the care because we do have a lot of patients that might have private insurance and their copay is really not reasonable for them and I use the word reasonable because what might be reasonable for me might not be reasonable for others. I mean, I can tell you I have one patient that was quite excited when his copay was $3,000 as opposed to $30,000.

[00:35:30] And then there are other patients that say, look, $500 a month is just completely out of my range given all of the financial burdens that they have. So I think those things definitely factor into it. We've seen individuals try to stretch out their therapies, splitting pills, et cetera, but I think hopefully cost comes down in the future. One thing that people like Martha and I, that we can really look forward to is that as we have
[00:36:00] newer therapies come on the market, the hope is that that will breed competition within the market, which I mean has the effect of obviously enhancing innovation, but also the beneficial effect on everybody else of lowering cost. But whether that plays out is unknown, I mean, I can tell you that when asked or on different scientific advisory board meetings, et cetera, or just talking with colleagues, I think one of the things that we really hope for is that costs come down. I think that's one of the key messages.

[00:36:30]
Dr. Palmer: Great. Martha, anything to add to that before we close or that key takeaways?

Dr. Grogan: I love that there are so many analysts in the financial world trying to figure out which drug is better. And they often use a lot of flawed thinking in my mind, what was the six-minute walk at one year? Well, I don't really care in a long disease, but I really do care what is the cost going to be for the patient? And that is going to drive choices of therapy, I think for sure. And there are very few people where a thousand or $1,500 a
[00:37:00] month is not some type of a burden, that they're not making people that have reasonable incomes, but they've worked their whole life and now they're retirement is all going towards this one drug and they're sacrificing things that they really want to do. So I think that is so important. We have to keep pushing. And this is not really a rare disease. So some of the pricing and some of these things are kind of hidden behind the veil of the rare disease. We don't know how common ATTR is, but we
[00:37:30] know that it's not rare. And so I think that's really important.

Dr. Grodin: And I want to just add really quickly to what Martha said. We have to recognize that a lot of these individuals are coming to see us and they're scared. They're looking things up online that may have to do with AL amyloidosis and they think it applies to them. And the cost, I think, can't be understated because as Martha alluded to, they really might be pulling resources to really try to pay for these treatments that really might be influencing or changing the way that they live or might influence some of the other
[00:38:00] plans or other things that they might have aspirations for that might also be important to them.

Dr. Palmer: So thank you both for sharing your expertise with us today. So let's review the takeaways from today's discussion. So Martha, what are the one or two things that you'd want people to remember from today's discussion?

Dr. Grogan: We didn't talk about it a lot, but I want people to make sure that they have the diagnosis correct. So there's all kinds of resources for that. And then the second thing is, honestly, this is just so exciting that we see that we have therapy and it works. We
[00:38:30] have challenges, but we have so many opportunities for our patients and it's an exciting field and every cardiologist should be interested in this, right? But really need to pay a lot of attention because it's rapidly changing.

Dr. Palmer: And Justin?

Dr. Grodin: Yeah, I think dovetailing with what Martha said, it's definitely exciting. And even this podcast and being invited here really underscores the enthusiasm for learning more about this disease and the improved recognition. And it's at least been a pleasure to [00:39:00] see that evolve over the last few years. And then the last point is, I do think that our treatments and our therapies are getting better and better. And then some of the areas that are uncertain, which Martha and I had tried to at least have a good time and speculate for you and try to chat with you about, some of those questions will be answered in really the not so distant future. And I really can't wait for that.

Dr. Palmer: So as we end this podcast, my key takeaway listening to these two experts is that, [00:39:30] there are still uncertainties in the testing of these patients following and even treatment in some regard, but there's still a lot of hope on the horizon. I mean, we have these treatments available to us, tafamidis and the ATTR silencers, and I think these uncertainties hopefully for the audience, have raised possible research questions that they can help to answer. And I think the last thing is that, we've done such great work in raising awareness and diagnosing this disease, and I think the next step is to improve access to those who are underserved and underrepresented. So [00:40:00] thank you both Dr. Martha Grogan and Dr. Justin Grodin for sharing your expertise in today's podcast. And thanks everyone in the audience for listening to our podcast. Stay and have a great day.