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### ASNC Presents: Cardiac Amyloidosis: Practice Essentials for Diagnosis & Management

Narrator:

Welcome to CME on ReachMD. The following activity titled, "Cardiac Amyloidosis: Practice Essentials for Diagnosis and Management," is provided by the American Society of Nuclear Cardiology and supported by an educational grant from Pfizer. Prior to beginning, please be sure to review the faculty information and disclosure statements, as well as the learning objectives.

Dr. Soman:

Hello, my name is Prem Soman. I'm a cardiologist at the University of Pittsburgh. We are here today at the American Society of Nuclear Cardiology at this roundtable discussion on cardiac amyloidosis. With me here are 3 other faculty who are experts in the field of cardiac amyloidosis. On my left is Dr. Mathew Maurer from Columbia, New York. On my right is Dr. Frederick Ruberg from Boston University, and Dr. Sharmila Dorbala from the Brigham and Women's, again in Boston.

This is an exciting time for patients with amyloidosis, their family, and their caregivers. A lot has happened in the field that has improved our understanding of the pathophysiology of cardiac amyloidosis, new techniques have evolved that facilitate an easy diagnosis, and most importantly, there have been exciting developments in the field of therapeutics. And now there is hope in an area where therapeutic nihilism previously existed.

So, Rick, what is cardiac amyloidosis, and why should we be so interested in it now?

Dr. Ruberg:

Well, Prem, so cardiac amyloidosis is a problem with protein folding. And so we all make proteins—our bodies make proteins normally—and sometimes those proteins misfold, and that misfolding pathology results in accumulation of a protein fiber called amyloid that deposits in visceral organs and other soft tissues of the body. As far as cardiac amyloidosis is concerned, when the amyloid deposits in the heart, it leads to the phenotype of a restrictive cardiomyopathy. There are 2 major proteins that misfold that cause cardiac amyloidosis. One of them is called immunoglobulin light chain—we relay that AL or amyloid light chain—and the other is called transthyretin, or TTR. We abbreviate that ATTR. And TTR amyloidosis is further subdivided into the genetic nature of the TTR protein. There's a hereditary form, which is abbreviated hATTR, and then there's a wild type, or genetically normal form, which we abbreviate ATTR wild type.

Dr. Soman:

So, Rick, we thought amyloidosis was a fairly rare disease. Is that concept changing?

Dr. Ruberg:

It is changing rapidly, actually, with the advent of newer diagnostic techniques that are accessible to clinicians that can raise awareness of disease. AL amyloidosis, I think, is definitively a rare disease. Reproducible studies have shown that it affects maybe no more than 5,000 to 7,500 new cases in the United States every year, whereas ATTR amyloidosis is probably much more common. We don't exactly know how common it is. One of the hereditary forms of amyloidosis has actually a fairly high prevalence in the African-American population. We abbreviate that as V122I, which stands for a nucleotide substitution at position 122 of the TTR protein. That particular genotype is prevalent in 3.4% of African-Americans, which translates to about 1.5 million people, of which about 150,000 are over the

age of 60 or 65 years old, are at risk of this form of amyloidosis. Wild type amyloidosis has been shown to be in as frequent as 10% of older patients with heart failure with preserved ejection fraction, and so it may be much more common. And we also know from autopsy studies that patients, as they get older, certainly over the age of 80 or 85, the prevalence of amyloid in their hearts increases significantly.

Dr. Soman:

Matt, you see a lot of patients with amyloid. Tell us, what are some of the challenges in making this diagnosis, and why is it so critical to make an early diagnosis of cardiac amyloidosis?

Dr. Maurer:

Yeah, well, I think it's actually not that challenging, from where I sit. I think people just never think about it. As Rick was describing, it's thought to be relatively rare and unusual, but in distinct cohorts: heart failure with preserved ejection fraction, older adults—older adults you presume have hypertrophic cardiomyopathy—individuals who are undergoing a transcatheter aortic valve replacement but have a low flow phenotype, those are people who we really believe are at increased risk, and the data seems to reproducibly suggest that somewhere between 10, 15, maybe even as high as 20% of those cohorts.

There are lots of clinical clues that we've all learned about. It's an infiltrative myopathy, so it results in increase in wall thickness with actually a relative reduction in the voltage on the QRS on EKG, so you have a voltage to mass discordance, if you will. That's one of the seminal and most sensitive (unintelligible)\*5:05 clinical characteristics that one can utilize to identify it. There are a whole host, as you all are well aware, of imaging characteristics on echocardiography, on MRI, but I think the thing that has really changed our perception is some emerging treatments that are actually much more effective, which we'll talk about, if administered early in the course of the illness. And then there's no doubt that nuclear cardiology has kind of revolutionized the diagnosis with the advent of scintigraphy that enables a diagnosis without a biopsy.

In the past, when the suspicion was high, people had to go on to aggressive and invasive biopsies, such as an endomyocardial biopsy, which was usually done just at rare specialized centers and required not only technical expertise in doing the procedure, but really required pathological expertise and kind of an interpreting, and that led to, I think, long delays in the diagnosis, which is changing rapidly now.

Dr. Soman:

And, Sharmila, what are some of the developments in non-invasive diagnosis that have, I want to say, almost revolutionized this field by facilitating an easy diagnosis? So, what is this technique that everybody's talking about?

Dr. Dorbala:

Yeah, absolutely. You're right, Prem. All of us have heard about bone scintigraphy. It has been around since the 1980s, actually, but only recently has it been recognized to be specific for the ATTR form of disease. This is an easily available radiotracer in the United States. It's technetium-99m pyrophosphate, also called PYP, whereas in the European countries, it's more DPD and HMDP. So, PYP is widely available in this country and easy to use. Typically, it has been used as planar imaging combined with SPECT imaging of the heart. And the most recent publication on this from 2016 from a multicenter study has now established in a large number of patients the diagnostic accuracy in terms of very high sensitivity and specificity in the right patient cohort with typical echo and CMR features where a monoclonal process has been excluded. So, this now makes this test accessible to most medical centers in the United States.

Dr. Soman:

So, that's a very nice story, a tracer that has been available for a long time, a tracer that's not very expensive. Is the test difficult to do, or can most laboratories learn how to do it?

Dr. Dorbala:

Yeah, I think the beauty of PYP imaging is, if you have access to the radiotracer, the test itself is very simple. Any institute and center that has a SPECT scanner can perform this test very easily. We use standard protocols. We use SPECT imaging as well as planar imaging with standard protocols.

Dr. Soman:

Now, Rick, you mentioned that there are 2 different types of cardiac amyloidosis, at least 2 types that encompass about 90 to 95% of the patients that we see. And does the PYP behave the same way in both of these patient populations?

Dr. Ruberg:

That's an excellent question. So, the initial experience with PYP imaging suggested that it was very good at differentiating the light chain AL from ATTR amyloidosis. And in general, that turns out to be true, although we have learned that there are a proportion of patients with AL amyloidosis who do have what is considered to be diagnostic uptake of PYP, suggestive of ATTR, and in that population one

has to be very careful. This is why the imaging test can't be interpreted alone clinically. The test has to be interpreted in conjunction with an assessment of light chain amyloidosis, which is typically performed by serum free light chain testing, serum immunofixation electrophoresis, and urine immunofixation electrophoresis. If those tests are normal and the pyrophosphate scan shows diagnostic uptake, based upon the consensus paper that Sharmila was just alluding to, you can diagnose somebody with ATTR amyloidosis without the need for further biopsy. Then you would appropriately go on to check the genotype of the patient to determine whether it was the hereditary or the wild type form.

Dr. Soman:

So, this ability to make a diagnosis without a cardiac biopsy, which, of course, is an invasive technique, has uncovered a prevalence of this disease that we didn't know existed. But, before I go to that, Matt, we have AL amyloidosis and ATTR amyloidosis, and though they're both cardiac amyloidosis, there couldn't be 2 diseases that were more different from each other. So, for our viewers, can you sort of elaborate on the importance of making this differentiation and how critical a clinical step that is in the process of making this diagnosis?

Dr. Maurer:

Yes, it's really key. These 2 diseases, while both causing "cardiac amyloid," are quite distinct. They differ, as Rick was saying, based on the biology of the disease. One is due to plasma cell dyscrasias and disorders; the other is due to misfolded transthyretin; so they differ with regard to their prognosis, their epidemiology, and ultimately their treatments, so it's critical to not misdiagnose someone who has AL with TTR or vice versa. We've known for a long time that AL amyloid, especially with advanced heart disease, is highly morbid, associated with median survivals measured in months, and so AL amyloid is really a medical emergency when you entertain it in your differential and requires a pretty expeditious workup. We like to ask people to assess for monoclonal proteins within a few days or a week in order to kind of establish a diagnosis and get patients hooked up if you're not comfortable with evaluating them to a specialized expert center. We've had treatments for AL amyloid for decades—anti-plasma cell therapy—that are quite effective if administered early. So, for both forms, it's clear that identifying the people early is important, but it's always been critical for patients with AL amyloid.

Dr. Soman:

So, to emphasize that again, as we work-up patients with suspected cardiac amyloidosis, differentiating the type of amyloid is perhaps the most critical part of the process. And as you mentioned, PYP scanning is much more sensitive for ATTR amyloidosis, but it is well-recognized that some patients with AL amyloidosis may show mild or sometimes even more than mild uptake of PYP, and so this really critical recommendation that the interpretation of the PYP scan is always to be made in the context of serum studies.

So, Sharmila, do you recommend that laboratories automatically order serum studies when PYP scans are done? And what is the ideal complement of tests that should be used to exclude a monoclonal process?

Dr. Dorbala:

Yeah, I think that's an excellent point that you raise. Not only is it important to diagnose transthyretin cardiac amyloidosis, but it's also important not to miss the light chain form of disease, which is the more acutely severe form of disease. So, in that context, I think different practices do it differently, but one way or the other, when you interpret a PYP scan, it's important to interpret it in the context of an underlying clonal process in the bone marrow, and typically that is done, as Rick had discussed before, by serum free light chain assay as well as serum and urine immunofixation electrophoresis studies. The most important thing I would like the viewers to know is reach out to your hematologist if you have any question about interpretation of these studies. You have the imaging folks helping you with the PYP scan interpretation, and for assessment of the plasma cell dyscrasia, don't hesitate to reach out to your hematologist.

Dr. Soman:

And the interpretation sometimes can be quite nuanced because you have things like monoclonal gammopathy of uncertain significance, or unknown significance, in patients of the same age group where ATTR wild type amyloidosis is prevalent, and mild abnormalities can occur in the context of renal failure, other nonspecific hypogammaglobulinemias, and so these tests are not always completely negative or completely positive, and so to partner with an experienced hematologist is really very, very critical. What about interpretation of the PYP scans? Are they usually black and white? Pun intended!

Dr. Dorbala:

Very much so. In my opinion, I think the negative scans are straightforward. Most people consistently read them as negative. The strongly positive scans are also straightforward on grade 3 where you see intense uptake in the myocardium and your SPECT images look like your myocardial perfusion SPECT images, so those cases are clearcut. The challenge may be in separating grade 1 and grade 2, and in those cases what I suggest the viewers do is closely look at the SPECT images. In fact, in any PYP scan, if the planar is positive, grade 1, 2, or 3, SPECT imaging is critical to understand whether the positive planar uptake is related to myocardial uptake of PYP or blood pool uptake.

Dr. Soman:

So, Sharmila, it's a fairly easy test to perform and widely available, so if a lab wants to start performing PYP's, where does it go for resources?

Dr. Dorbala:

That's an excellent question. For all the viewers who would like to start diagnosing transthyretin amyloid early using PYP imaging, I encourage you to do so. The American Society of Nuclear Cardiology, ASNC—go to the ASNC website. There's an amyloidosis resource page on ASNC website, and there are a lot of other resources for PYP imaging available there, so I strongly encourage you to look at that.

Dr. Soman:

So, Matt, now we have this technique with which we can make a fairly confident diagnosis in the vast majority of patients. We don't need a biopsy. So, what has that done to our understanding of disease prevalence?

Dr. Maurer:

Yeah, it's dramatically altered it, as we were mentioning previously. There are seminal studies that have recently been published, and while the exact prevalence of TTR is unknown, the highlights are that 13% of people in the hospital with HFpEF and increased wall thickness basically had wild type TTR diagnosed by a cohort study done in Spain. About 5% of people who are presumed to have hypertrophic cardiomyopathy were allele carriers. In theory, mutations that the people thought were in the sarcomere had HCM—have amyloid I should say. In fact, amyloid is probably the most common phenocopy and mimicker, if you will, of HCM in people over the age of 60. Certainly, there are even more alarming data that if you just do scintigraphy on a healthy cohort of individuals over the age of 75, it's about 1% of women and 3% of men, essentially, have myocardial uptake consistent with the diagnosis, so it's an age-dependent phenomenon. The largest growing cohort of people in the world right now, believe it or not, are those over the age of 85, given the successes of modern medicine, and so this will only, I think, increase dramatically over time.

Dr. Soman:

Those are extraordinary numbers of a disease that... I remember growing up, going to medical school, when there was a case of cardiac amyloidosis, everybody went to see this patient because you never saw this. And in our newly established amyloidosis clinic at the University of Pittsburgh, we're seeing 2 to 3 new patients every week. Is that sort of your experience? You have a more established center, so what are the sort of numbers that you see with TTR amyloid?

Dr. Maurer:

Oh yeah, we're seeing 5 or 10 new patients, potentially, every week is possible. The other part, I think, for practitioners to really understand is, as you're indicating, this went from a diagnosis that was a zebra to one in which essentially you're encountering a patient a day probably in a very busy cardiovascular practice, especially if it's focused on older adults, so it's there if you look for it.

Dr. Dorbala:

Yeah, and I agree. I think PYP imaging has made it possible for us to look for TTR amyloid before the patient has developed advanced heart failure manifestations. So, before that, we had to use endomyocardial biopsy and people were not doing it until you had a reasonable suspicion of amyloid, but now with PYP imaging, we're able to screen for TTR amyloid.

Dr. Maurer:

And that's a critical time point, right? Because all of the emerging therapies that we're all very excited about, essentially to date, as far as we know, work in a preventive manner. They prevent new amyloid deposits. They don't, that we're sure of, eliminate existing amyloid, and so early diagnosis is going to be critical to therapy success.

Dr. Ruberg:

I would also add the PYP imaging has changed our understanding of the disease and its demographics. Studies have shown that if you actively look for patients with PYP imaging, the number of women identified with disease has increased. Traditionally, this disease has been described in almost... Most of the cohorts have described it in 95%, where men—most of them were white men, and studies looking at PYP imaging have begun to change that. And I would also say it also has changed our understanding of the kind of the distribution phenotype. We understand now that patients sometimes have a symmetric septal thickening, which we didn't see before, as identified by PYP imaging and kind of identified people who otherwise wouldn't have been thought of for cardiac amyloidosis. So, I think the advent of PYP, not only has it changed the relative distribution of the types of amyloidosis patients seen that are referred, it's also changed our understanding of who this disease affects.

Dr. Dorbala:

And for the first time we may be able to evaluate epidemiology using a non-invasive method.

Dr. Maurer:

And to follow up on Sharmila's point, which I think can't be underemphasized, it's changed the phenotype. So, in our center, people who are diagnosed now by PYP scanning have earlier disease. They're New York Heart Class is on average median II, not III. Their wall thickness is on average 14 mm, not 17 mm. Their biomarkers are lower. I don't think we've done anything to change the natural history of the disease. I just think we've now enabled providers to have a technique that identifies people with an earlier phenotype, which, again, will be critical to therapy.

Dr. Ruberg:

And it's permitted us to diagnose patients like the low-flow, low-gradient AS patients that Matt alluded to. We now have ways to look in an acceptably safe way for new cases and emerging demographics that we otherwise wouldn't have thought about.

Dr. Soman:

So, I just want to step back a little bit now. In centers like your centers where there's a high awareness, the diagnosis is probably made much earlier than in the community where there is still a long lag time before the initial presentation to the physician and the diagnosis. We have the tools to make the diagnosis, but we have to think of the diagnosis. So, if there is one message that our viewers should take home today, that is that you think of amyloidosis, it's much more prevalent than we thought, and that is the first step towards making the diagnosis.

Matt, you've led some of the seminal therapeutic trials in this field. Can you sort of give us a synopsis of what the lay of the therapeutic land looks like for cardiac amyloidosis?

Dr. Maurer:

Yeah, it's been a collaborative effort from everyone here, and other people throughout the world actually. It's pretty exciting. So, in general, there are 2 main strategies that have now been shown to be effective for transthyretin amyloid, and those are the concept of silencing—that is shutting off the production of the transthyretin protein at the liver. There are 2 therapies that are approved in the US: for example, patisiran and inotersen, both working by knockdown therapy. One is a small interfering RNA, and the other is an antisense—administered in slightly different fashion but have unequivocally been shown in patients who had hereditary TTR involving the nerves, in 100% of the people in the trial, many of whom had concomitant cardiomyopathy, but their clinical indication at this point is for patients who have a neuropathy due to TTR with or without a cardiomyopathy. Those agents clearly slowed the progression of the neuropathy, if not maybe even halt the progression of the neuropathy. And they're pretty exciting, and there is great hope for those particular therapies to even help in patients who have a pure cardiomyopathy, such as the wild type patient, or the majority of patients who have the V122I mutation. So, that's one strategy.

The second is so-called stabilization. That is the idea of preventing the protein from falling apart. And in that regard, while there is a nonsteroidal that we have used off-label for many years called diflunisal, tafamidis is kind of the new kid on the block. Tafamidis is an oral molecule, so it's a once-a-day agent, unbelievably safe, as shown in the ATTR-ACT trial in which, when administered to a moderate-sized cohort of 441 people, reduced mortality overall by 30 to 33% and reduced cardiovascular hospitalizations by a similar amount. So, kind of on a practical clinical level, the data from the ATTR-ACT trial are kind of unbelievable in that if you administer tafamidis to 7 or 8 patients over 30 months, you'll prevent 1 death, and if you administer it to 4 patients, you'll prevent 1 hospitalization over just a year's time. So, these are absolute reductions in events that haven't been seen in a cardiology trial for a long period of time. And there are other agents that are soon to be in late-phase clinical trials or are in late-phase clinical trials that hopefully will increase the armamentarium quite a bit.

Dr. Soman:

So, the results are quite staggering, very positive, particularly in the field of heart failure where big successes are not the norm, right? So, this is really good news. And so, the planets are aligned, so to speak. We have this recognition of a very high prevalence of the disease, an ability to make the diagnosis noninvasively, and a bunch of new therapies—the best possible situation. So, thank you all for being here and talking to us today.

Dr. Dorbala:

Thank you.

Dr. Maurer:

Thank you.

Dr. Ruberg:

My pleasure, thank you.

Narrator:

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