Dr. Renee Bullock-Palmer (00:02):

Welcome to the American Heart Association ATTR: Closing The Knowledge Gaps in Transthyretin Cardiomyopathy podcast series. I'm Dr. Renee Bullock-Palmer and I will be leading the discussion today on the second podcast in the series titled "Diagnostic Imaging Strategies for Cardiac Amyloidosis". I'm the director of the Noninvasive Cardiac Imaging as well as the Women's Heart Center at the Deborah Heart and Lung Center in New Jersey. This series is intended to increase the ability of healthcare practitioners to recognize and provide for early identification of patients with transthyretin amyloid cardiomyopathy, commonly referred as ATTR cardiomyopathy and to also ensure accurate diagnosis and timely initiation of their proper treatment therapies before the onset of cardiac dysfunction. Being able to make the correct ATTR diagnosis and devise a treatment plan is grounded in understanding the life-threatening pathophysiology of cardiac amyloidosis and engaging in evaluative strategies for earlier detection.

(00:58):

Before we begin today's podcast, let's review the learning objectives that's specific to this podcast. Our first objective is to describe the latest recommendations in diagnosing cardiac amyloidosis through cardiac imaging. Secondly, to outline how scintigraphy of bone avid radiotracers should be performed and interpreted to avoid misdiagnosis. Secondly, to outline the diagnostic imaging strategies with regards to differentiating ATTR from AL cardiac amyloidosis. And then followed by outlining the role of cardiac imaging with regards to screening family members for familial ATTR cardiac amyloidosis. Then we'll also discuss on how to determine in response to treatment for cardiac amyloidosis through cardiac imaging. Lastly, we'll outline the latest developments and future direction of imaging for cardiac amyloidosis.

(01:45):

We're joined today by our distinguished colleagues, Dr. Ahmad Masri and Dr. Frederick Ruberg. Dr. Masri, why don't we start with you introducing yourself.

Dr. Ahmad Masri (01:53):

Great. Hi, Dr. Bullock-Palmer. Thank you for having me here today. It's a pleasure to join you and Dr. Ruberg. My name is Ahmad Masri. I'm a cardiologist. I'm an imager. I direct the Cardiac Amyloidosis Program at Oregon Health and Science University.

Dr. Renee Bullock-Palmer (02:07):

Dr. Ruberg, please introduce yourself.

Dr. Frederick Ruberg (02:08):

Thank you so much, Dr. Bullock-Palmer, and it is a pleasure to be here today with you as well as Dr. Masri. I'm at the Boston University Amyloidosis Center. I'm the Associate Chief of Cardiovascular Medicine at Boston University, and I have been affiliated with the center since 2005. I'm also a cardiac imaging specialist, particularly in echocardiography and cardiac MR. I'm quite interested in imaging for the diagnosis and treatment of cardiac amyloidosis.

Dr. Renee Bullock-Palmer (02:32):

Great, thank you both and welcome. Dr. Ruberg, as you know, there is a joint multi society, ASNC, AHA, ASE, as well as HFSA guidelines, The Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis and this was published in 2021. Could you describe the recommendations and how

you go about using cardiac imaging to diagnose your patients with suspected cardiac amyloidosis and what is your first go-to test and where do you go from there, Dr. Ruberg?

Dr. Frederick Ruberg (02:58):

Thanks, Renee. It's a great question. So as we all know in 2023, the principle way in which we make the diagnosis of cardiac amyloidosis now is mostly through imaging. And so these consensus guidelines that were led by Dr. Sharmila Dorballa and Jamie Bourque really helped us understand how to perform, interpret, and also the appropriate use scenarios where these tests could be useful. We have to take a step back and always remember that endomyocardial biopsy is still a very indispensable test, which we'll talk about I believe later in this podcast, in situations where the imaging doesn't add up or the imaging and the non-invasive blood testing doesn't add up. And it's particularly helpful for also identifying less common or rare forms of cardiac amyloidosis.

(03:38):

But generally speaking, in imaging we have three options: echocardiography, nuclear scintigraphy and cardiac MR. The first two tests, echocardiography and cardiac MR are themselves not diagnostic of cardiac amyloidosis without a biopsy, still in 2023 whereas scintigraphy is. Echocardiography is the first line imaging test for almost every patient with cardiac amyloidosis. But the findings can be nonspecific and often overlap with other wall thickening hypertrophic diseases like hypertensive cardiomyopathy or hypertrophic cardiomyopathy. Generally in echocardiography, patients have diastolic dysfunction, increased wall thickening, and one key to echocardiography is abnormal global longitudinal strain, particularly the ratio of the apical strain segments to the basal strain segments, which generally exceeds two or 2.1 or an abnormal global longitudinal strain to LVEF ratio that exceeds four. Those are useful but not in themselves diagnostic.

(04:28):

Cardiac MR is indispensable. In cardiac MR, you see global longitudinal LGE in a subendocardial or transmural pattern and increased extracellular volume fraction. Extracellular volume fraction typically exceeds 40% in cardiac MR with amyloidosis. But in itself, CMR is still not diagnostic without additional extracardiac or a cardiac biopsy.

(04:48):

Now nuclear scintigraphy is different because the test has been validated now in multiple different studies, most significantly, one that was published in circulation in 2016 by a multinational group demonstrating that nuclear scintigraphy using PYP, DPD or HMDP imaging can be diagnostic for cardiac amyloidosis in the context of uptake that is consistent grade two or three uptake or and in the absence of evidence of light chain abnormality on blood testing. So only in that context when the blood testing demonstrates no light chain abnormality and the nuclear testing is diagnostic demonstrates grade two or three uptake, can we diagnose cardiac amyloidosis without the need for a tissue biopsy. That said, there are a number of caveats to how these tests are performed that we'll discuss later on in this presentation.

(05:32):

So in my mind, my first go-to test, certainly in somebody who's older, in older, I would say over the age of 60 because that's the age in which ATTR amyloidosis typically manifests. I would start with a nuclear imaging PYP or DPD scintigraphy. Whereas in a younger person where AL amyloidosis is more likely to be manifest, I would probably start with a cardiac MR after echocardiography is done in all people. So that's kind of my general overview of how I'd approach these advanced diagnostic imaging tests and echocardiography in the diagnosis of ATTR or AL amyloidosis.

Dr. Renee Bullock-Palmer (06:04):

Thanks for that very comprehensive answer. So Dr. Masri, I know that you direct the Cardiac Amyloidosis Program at your center and several institutions have started similar programs. So as a cardiac imager, what are the key cardiac imaging services required to build these programs successfully and what are the roles and responsibilities of the cardiac imager in such programs, Dr. Masri?

Dr. Ahmad Masri (06:22):

Great question. I think Dr. Ruberg touched base on many of these aspects. I think the first thing to remember is clinical assessment is very, very important. And the second thing to remember is that amyloidosis is actually the exemplary diagnosis that is imaging based in general with exceptions, and it does require a lot of careful assessment.

(06:44):

And so if I am to summarize, I think the first thing is having good echocardiography services that actually apply strain imaging for LVH. I think this is important because patients don't come to us and say, "I have amyloid." They just come with LVH and without doing strain sometimes even if the picture on 2D looks like amyloid, it still gets missed. So strain is more or less a reminder that we should think about amyloid that's one.

(07:10):

The second thing is cardiac MRI, which is it requires a lot of investment to be able to do really good quality or high quality cardiac MR. But I would submit that I think like Dr. Ruberg said, in patients who are not the classic older patient phenotype, someone who's coming with LVH with half death, with a lot of heart failure, CMR is fantastic to work up amyloid and other diseases. So you can not just only exclude amyloid, but you will do it all. And so that's the second test.

(07:43):

The third test is, or the third modality is nuclear imaging. And so that's essentially is SPECT or SPECT/CT if you're doing clinical work because you need the SPECT imaging if you are doing bone scintigraphy. Nobody should ever do bone scintigraphy without SPECT. And in my opinion, even for negative scans in general, unless you are sitting there triaging the results, you probably still need SPECT in the majority of these cases. And so, or PYP, HDP, HLDP or DPD and whatnot. If you're doing research, obviously you would need the PET program as well at the same time because there are a lot of PET tracers.

(08:22):

And then finally, CT coronary. While in general, we do not need CT scans in patients with amyloidosis. I think there are many papers showing how these patients have valvular heart disease. You sometimes need actually transcatheter interventions in these patients. Aortic stenosis is a primary example, but more or so lately, mitral regurgitation, tricuspid regurgitation. So you need structural heart team that can support you also with good structural CT for these specific types of problems that you encounter.

Dr. Renee Bullock-Palmer (08:57):

Great. Wonderful. So Dr. Ruberg, with more and more institutions performing cardiac scintigraphy studies with bone avid radiotracers and increasing awareness of ATTR cardiac amyloidosis, there is a growing concern for misinterpretation of these studies and therefore misdiagnosis of these patients. This has far-reaching implications, as you know, with medications being used to treat these patients being very expensive. So what are the pitfalls to watch for when you're interpreting these studies and what are the common causes of misinterpretation, Dr. Ruberg?

Dr. Frederick Ruberg (09:24):

Thank you. That's an extremely important question and Dr. Masri's already highlighted the importance of having experience in the imaging services, and I think that that really speaks to helping reduce the likelihood that imaging might be misinterpreted. Well, we covered a lot of these important pitfalls in a recently published expert consensus decision pathway document that was published from recently in the Journal of American College of Cardiology. And there we outline some of these pitfalls that I'm going to elaborate right now.

(09:50):

The first error I think people make is that they acquire scintigraphy or image or even CMR in the wrong clinical scenario, and not really consistent with amyloidosis. One shouldn't really be ordering a nuclear scintigraphy or PYP imaging for amyloidosis in somebody with a dilated cardiomyopathy. Most cardiomyopathy phenotypes should generally look like amyloid disease. Granted, there are certain situations in which certainly in end-stage disease patients may or may not develop different types of cardiac phenotypes, but in any case, one should frame the application of imaging to the right clinical scenario.

(10:23):

The next problem that people often get into is that they perform planar imaging only and they don't do SPECT. I think that that's hopefully vanishing a bit. The most recent ASNC recommendations include favor for SPECT/CT because that decreases the likelihood of misrecognition of blood pool tracer. But failure to perform SPECT or a SPECT/CT often leads to a misdiagnosis because many patients could have what appears to be diagnostic uptake on the planar image, but it will be a blood pool.

(10:49):

The third is to really over rely on the heart to contralateral ratio for diagnosis. The heart to contralateral ratio is a ratio of the number of counts of the heart over the contralateral chest, and that is quite a variable ratio. And there was certainly a lot of enthusiasm about it. I mean, my own group and colleagues have published a fair amount on it, but I feel like it's meant to be used in the context of the semi-quantitative assessment and not used in isolation. So rely upon relying upon that alone is kind of fraught with the possibility for error.

(11:20):

The next problem people run into is that they order the wrong kind of light chain testing. So we've talked about how one can misinterpret imaging. One can also misinterpret light chain testing and therefore miss light chain amyloidosis, which can appear as ATTR amyloidosis and even have diagnostic appearing uptake for ATTR in about 10% of cases. So not ordering the right light chain tests, which include serum free light chain levels, concentration and immunofixation electrophoresis of the plasma and urine and SPEP is a test that people often first order, but that is insensitive for the lower paraprotein burden that's most common in AL amyloidosis. So ordering an SPEP and getting a normal SPEP result and saying the patient doesn't have AL is a mistake or failing to recognize the abnormalities in either the immunofixation or the free light chain ratio was also a mistake.

(12:07):

The last thing I'll say is that we've seen a lot of false positive results now because we're now taking a test, PYP imaging and DPD imaging that was validated in a high prevalence population and now applying it in more screening lower prevalence populations where it's more likely to see false positives or less likely false negatives. In that case, it becomes really important to adhere to the best practices for how these tests should be performed.

Dr. Renee Bullock-Palmer (12:31):

Great, thanks. So Dr. Masri, there was a shortage of technetium PYP last year and several nuclear labs had switched to other bone avid radiotracers such as technetium HMDP. So could you explain to our listeners if there is any difference in performing and interpreting bone scintigraphy studies with PYP versus HMDP, Dr. Masri?

Dr. Ahmad Masri (12:49):

Great question. One thing to remember is that not all bone tracers are equal or equivalent, and that one needs to be careful which one they reach out to. There are only three that are known to be consistently positive in transthyretin amyloidosis. They can also sometimes be positive in light chain. That's why you need to rule out light chain. But at least from a TTR perspective, they are PYP, DPD and HMDP.

(13:18):

A quick note that MDP is not a tracer that you can use for transthyretin amyloidosis and we and others have shown that before. And HMDP, you can find it sometimes in your local pharmacy as HTP. So there are these differences in naming and nomenclature.

(13:37):

Now, there is really no major difference between the utilization as long as one is familiar with the tracer that they're using, they know how to handle it and they know how to look at the images. If you have SPECT/CT, you're invincible essentially. Everything is easy in a way. You can do one-hour imaging, two-hour imaging, three-hour imaging, and you'll still be okay.

(13:57):

The problem is that if you are using an old camera or if you're using SPECT only imaging, that can be sometimes difficult. And so for example, that's why three-hour imaging from an image quality perspective with HMDP sometimes is preferred over one-hour imaging or PYP, some centers prefer also three-hour imaging over one-hour imaging. I can tell you we've done it all. We've tried all of them. With a SPECT/CT, one-hour imaging, short wait time, the images almost always work out really nicely. But that will require you to have a SPECT/CT, not just SPECT only.

(14:35):

And then the other thing to remember is that the data we have majorly come from PYP and DPD, not from HMDP. So while we can use it for diagnostic purposes, it might not be the same for the future to use it for like other reasons. For example, now there are some efforts to quantify some of the uptake that we see. Logic dictates that it will apply also to HMDP, but we are not sure. But the message is the same, that it's safe to use this tracer in the workup of patients with cardiac amyloidosis, specifically transthyretin amyloidosis.

(15:10):

And if you are in doubt, you have a negative scan or an equivocal scan and you are clinically, the patient looks like they have amyloid, you should never stop even if it's PYP or DPD or HMDP. You should always pursue alternative modality, either a different imaging test or even biopsy if it comes to it. Never stop at bone scintigraphy and no PYP is coming back. But I can tell you it was a nice surprise how good the image is with HMDP HDP are. And we actually are now using, even though PYP is back, we are actually using more HMDP in our practice, especially in patients with lower suspicions because the target to background is a bit more crisp with HMDP compared to PYP in our scans.

Dr. Renee Bullock-Palmer (15:58):

Yeah, I was really happy to hear that last part because I actually in my own experience here at Deborah, we have actually switched to HMDP, so we no longer use what PYP and we have found, I mean, I haven't read an equivocal scanning quite a while with HMDP. It's either negative or positive. It's very clear. Great, thanks.

(16:15):

So as for, Dr. Ruberg, could you describe how you go about differentiating ATT or cardiac amyloidosis from AL cardiac amyloidosis with cardiac imaging, particularly when the bone scintigraphy test result is equivocal? How often do you rely on the endomyocardial biopsy, Dr. Ruberg?

Dr. Frederick Ruberg (16:30):

Super important question because this is a kind of common scenario, and I think with scintigraphy, it's really easy when it's grade zero or even grade one, it's pretty simple. And when it's grade three, it's pretty simple. And the problem is are those people who are in the middle when their equivocal testing results, the heart to contralateral ratio doesn't really help you all that much. So that's one scenario. The other scenario is when the light chain testing is abnormal, either the free light chain ratio or the immunofixation electrophoresis, what do you do?

(16:56):

Well, I mean, so Dr. Masri's already pretty much laid out the answer for you. And that is you continue further with either additional imaging or you move on to biopsy. And biopsy really has a role primarily in the evaluation, I'd say primarily of people who have abnormal plasma cell testing results and either have diagnostic uptake or don't have diagnostic uptake on PYP but one still suspects cardiac amyloidosis.

(17:19):

So this is where CMR though can be helpful because the presence of monoclonal gammopathy in older people is fairly high. Maybe 10% of people as they approach the seventh or eighth decade of life have some abnormalities. And even in our population of patients at Boston, University of Boston Medical Center, we looked at the PYP and light chain testing results and people referred by PYP and about a quarter of them had some abnormal testing result. So it gets to be pretty common in differentiating those patients can be difficult.

(17:46):

And the guidelines would suggest that you consult with hematology and or consider a biopsy. So the principle at time, I think we move on to endomyocardial biopsy is when we have this discordance between the blood testing result and the imaging. Unfortunately, imaging is not particularly good at telling you whether someone has AL or ATTR if they've got cardiac amyloidosis, at least I would say the imaging that we have now, we can talk about the PET tracers a bit later in this podcast because there may be some more information there.

(18:12):

But as far as the available imaging agents we have now echocardiography, there's generally a fair amount of overlap. The general principle is that because ATTR has a slower developing process, patients tend to have thicker walls, increased wall thickness, increased myocardial mass, and they may have more elaborate late enhancement or greater discordance say in the appearance of their imaging versus their clinical phenotype. That's more of an integration sort of point. But by and large, you can't use echo or CMR essentially to differentiate between AL or ATTR with some studies reporting otherwise, but not extensively validated.

(18:47):

So you really need to do the light chain test because 98% of patients with AL amyloidosis will have some abnormal light chain test result, but not all and you need to integrate those two. And you should always move on to biopsy when you're highly suspicious of one disease or another that's not entirely clear.

(19:03):

So just to review the light chain testing to make sure everybody is kind of on the same page there. Again, the testing is free light chain ratio, and that's a ratio of the kappa to lambda light chain. The kappa light chain is in the numerator, and that number can get higher in the context of chronic kidney disease because the kappa light chain is principally cleared through the kidney. So as EGFR drops, the light chain ratio increases and that ratio can increase to as high as three to even 3.3 or 3.4 in the context of advanced kidney disease without the evidence of an abnormal plasma cell dyscrasia. That said, when you start getting into that sort of range, I believe consultation with hematology is appropriate based upon your experience.

(19:44):

When the free light chain ratio is below the range of normal, that indicates a lambda abnormality and that is almost always something that should be followed up. Most cases of AAL amyloidosis are lambda, and so anybody who has a lambda plasma cell disorder by free light chain testing or by immunofixation electrophoresis should be consulted with a hematologist because they could have a lambda MGUS or they could have lambda AL amyloidosis.

(20:07):

So that's the most common scenario, which I think we think about, about biopsy. The less common scenarios are those in which there is really suspect suspected rare types of amyloidosis, the apolipoprotein amyloidosis or the gelsolin amyloidosis even more uncommon. These are scenarios in which I think biopsy is really the only way to make the diagnosis.

Dr. Renee Bullock-Palmer (20:29):

Wonderful. So Dr. Masri, with patients that are coming increasingly aware of the hereditary nature of ATTR amyloidosis, could you outline the role that imaging plays with regards to screening family members for this familial form?

Dr. Ahmad Masri (20:40):

So just to get some things out of the way, I think we should really focus on some disease states or maybe not even disease states, just nomenclature, which is being genotype positive does not mean that there is disease or the disease will ever develop. I think a lot of patients or even physicians fall into this trap because it's an autosomal dominant disease. They always think that the patient will develop disease. That's not true. And then the current approach to diagnose the phenotype is fully imaging based. We don't rely on biochemical testing, which is stability of TTR or TTR level to actually diagnose the disease because we don't have studies to show exact relationship between unstable TTR and phenotype development. And so that's the second thing. The third thing is that we do not recommend treatment for genotype positive, phenotype negative patients. So what does that mean? That means that all of these patients will fall on imaging for surveillance.

(21:38):

And so the way that imaging works in this space is it's still in a way expert consensus or expert-driven, not really based on a lot of long-term longitudinal studies, but for at least in our practice, what we do is that we recommend that patients start about 10 years before the onset of disease in their family member. Meaning that not when they were diagnosed, no, when they developed symptoms, their

family member, when they developed symptoms, they start 10 years before. If the family history is unknown, then for some mutations 40 years old is reasonable, for others, 50 years old is more reasonable. And then we evaluate patients once every 18 to 36 months. We do clinical evaluation once every 18 or 24 months, and then we do an imaging test once every three years.

(22:31):

I think in general some people like to do bone scintigraphy. I think that's a lot of radiation, a lot of bone scintigraphy testing. So what we have done more is EKGs and echoes, and then if we see a suspicious phenotype, then we can do more imaging tests with PYP or HMDP. If the patient has symptoms, we work them up as having suspicion for disease, even if the echo is not classic. And we have had cases where the echo is not classic, but the other imaging tests were very positive for transthyretin amyloidosis.

(23:09):

And lastly, one thing to remember is that for V122I, which is a popular or well-known variant, that is very, very common in patients of African descent, Afro-Caribbean descent, its prevalence is 3.4% of patients of African, Afro-Caribbean descent. But the phenotype manifests at a later age when it's heterozygous, which is the most common phenotype. And so typically, we start looking at imaging these patients towards 55 to 60 years of age, not earlier.

(23:41):

We had previous conversations seeing that now patients are testing their children for TTR variant, gene variant and starting even surveillance, which is not needed unless in rare, rare scenarios. This is an adult onset disease that is age related. And while imaging is viewed as non-invasive way of looking at the disease, it still carries cost and potential harm sometimes if it involves radiation or administration of contrast agents. And so while again, imaging is central here, I think you have to integrate clinical story, the clinical scenario, and the family history to guide testing over time.

Dr. Renee Bullock-Palmer (24:26):

Wonderful. So Dr. Ruberg, how do you determine a patient's response to treatment for ATTR? Is the role for serial cardiac imaging, I know Ahmad touched on this just now, and if so, what's the frequency intervals and what modality do you use to image your patients?

Dr. Frederick Ruberg (24:42):

This is a great and important unanswered question because we presently have one approved therapy for cardiac amyloidosis now, and we hopefully will have others if the clinical trials that are testing their efficacy are positive. So it will be really important to determine whether a drug is effective because that will help select whether or not a patient stays on that drug, transfers to another drug or adds drugs to demonstrate the best efficacy. And I think that there are a lot of ways in which we can look for readouts on how drugs are working. And there are obvious things like whether a patient's been hospitalized or not or things like how a patient feels, their NYHA classification, and there are other things that are being explored like changes in cardiac biomarkers or changes in their, say, their quality of life as assessed by the KCCQ score.

(25:25):

But imaging really affords a very attractive way in which to follow people because you are really looking directly at the heart and the progression of disease or the regression of disease as we'll talk about maybe with the advent of antifibral therapies, how those drugs are actually working, are they really

changing the function of the heart that then therefore translates into improved symptoms of heart failure and improved outcomes?

(25:51):

And so what are the options? Well, a lot of emphasis in imaging has been focused on diagnosis. One time imaging, make the diagnosis and you're done. Now echocardiography is very attractive as a serial imaging modality because it's easy to perform, it's relatively inexpensive and doesn't have any, it can be taken to the patient and it's easy for the patient and it's safe.

(26:12):

And so one metric that's been explored is changes in global longitudinal strain. Now in the ATTR literature, we know that the TTR stabilizers can stabilize strain. They keep it from getting worse certainly, and those who are untreated get worse. But we don't have any good data looking at serial changes in ATTR, unlike in AL amyloidosis where we actually have pretty good data in a number of single standard studies demonstrating that patients actually can develop even improvement in global strain with treatments for treatment for AL amyloidosis. So we need those data in ATTR and those are in development and it's hopefully forthcoming soon.

(26:48):

Cardiac MR, also even more attractive in some ways because you're looking directly at the interstitium and theoretically if you can stop the production of amyloid and there's some degree of regression, you can see that on the cardiac MR. And again, there aren't really good data in ATTR amyloidosis, but in AL amyloidosis there are better data looking at improvement in extracellular volume fraction, maybe 5% being a reasonable threshold has been reported by the National Amyloidosis Center in London that patients who are on the TTR stabilizer patisiran, most of them taking the TTR stabilizer diflunisal concurrently, a subgroup of about 16 patients had some degree of regression of extracellular volume, which was inferred to be a regression of amyloid fibrils that was associated with improvement in six-minute walk distance and biomarkers.

(27:32):

And so using serial MR might be a way to go, using serial echo might be a way to go. And then there's nuclear imaging. So we talk about semi-quantitative PYP, DPD, but there are ways of course to quantify using SPECT/CT and to standard uptake values maybe changes in that over time. Although again, those data are really more in single time points, snapshots in time, not really serial studies that might demonstrate regression. And I think this change in amyloid deposition over time with ATTR is going to be critical because we will soon hopefully have agents that might facilitate the degradation of amyloid fibrils or at least stop the production might permit some degree of resorption. And it'll be really important to understand how those drugs are actually working at the tissue level as well as how they might affect improvement in more qualitative outcomes of how people feel or quantitative quality of life or functional capacity or overall outcomes.

Dr. Renee Bullock-Palmer (28:28):

That's a wonderful answer. So this segue is nicely into the question to Dr. Masri. So what's the role, if any, for cardiac PET imaging for cardiac amyloidosis? Additionally, several nuclear labs have acquired CCT SPECT cameras. How do we perform these bone scintigraphy studies with these studies, with these cameras and interpreting these studies? And lastly, are there any novel applications with these cameras that may improve diagnostic accuracy and can be used to follow treatment, so Dr. Masri?

Dr. Ahmad Masri (28:57):

I'll try to answer these questions. Some of them are still undergoing rigorous investigation, but I'm a PET enthusiast because I think this is the next jump in the amyloid space. We have wonderful tools to diagnose the disease. I think one of the problems that we have is that we diagnose organs. We don't diagnose the whole body involvement with the condition. That's one. And the second problem is that we don't have reliable ways of tracking the disease over time. And so we think we do, but it's really not been put to the test essentially with large multi-center studies. And so I think with PET, the promises that we have had a long experience with different PET tracers and different indications, we know that we can in a way, in a reliable way, track PET tracer over time. We know that it's not just about myocardial uptake, it's also extra cardiac uptake. So you can transform an amyloid doses from just being a single organ problem at the time to understanding what other issues patients could be dealing with and looking at other organs.

(30:00):

And then finally, if there's going to be antifibral therapy, if there's going to be therapies to regress the disease, you would want reliable imaging agents that you can track over time and understand what's happening to them. Is it true amyloids removal or is there something else going on?

(30:16):

So that's my thing about PET is that I'm very excited about it. I think the next three to four years will really provide us with a lot more information and data about this. The final thought is PET tracers. Some of them tend to be pan-amyloid. And so it's truly in a way a one-stop shop so that you don't have to think about three, four different imaging tests. If you consider amyloid regardless of the type you can do then this PET scan. If it's negative, you're done. Now that needs to be proved. It's not really yet proved that this is the case, but that's at least the promise.

(30:48):

In terms of the CCT SPECT cameras, I don't currently have them in my practice. In my previous practice, we did. They are a recent development, a couple of years now. They are big improvement over the traditional angle camera. These systems have 360 degree coverage. They have favorable attributes such as higher spatial resolution, better count sensitivity, and contrast-to-noise ratio. They can acquire over shorter period of time. Patients don't have to lay flat. Some systems cannot actually perform planar imaging. So you are stuck with SPECT imaging only when it comes to that.

(31:21):

But in reality, from a diagnostic perspective, we use them interchangeably with regular angle cameras or with SPECT/CT. Now when things might change is that if we actually are able to start quantifying the uptake of PYP or other bone tracers on SPECT imaging, then CCT SPECT, there is a lot of work happening right now in working on quantifying the uptake there. And so this might be a different discussion, but that's where the promise is. But as of now, we just use all these systems in a way the same just because nuclear scintigraphy remains mainly a diagnostic test at this point in time.

Dr. Renee Bullock-Palmer (32:01):

Great. Wonderful. So Dr. Ruberg, what are some of the latest developments and future directions for imaging for cardiac amyloidosis?

Dr. Frederick Ruberg (32:08):

Thanks, Renee. I think we've touched upon a lot of them already. Ahmad already introduced the concept of PET imaging that I also alluded to previously. And I think that that's really one of the major kind of features of what we should look for in the future. Just to remind everybody, these PET avid agents that

are typically the ones that have been FDA approved but not for imaging cardiac amyloidosis are 18F tracers, and they basically have been approved for imaging brain amyloid and Alzheimer's disease, but also many of them have different properties than with cardiac amyloidosis. Those agents are not yet covered for reimbursement, which is why they're not utilized clinically. There are other imaging PET agents that are also in development that are being tested that will also likely be effective and hopefully add to our capacity to identify all patients with amyloid and not just as Ahmad said, "ATTR only or AL only."

(33:01):

And the other area that we've touched upon both is the advent of antifibral approaches. So we're so fortunate that there's been an explosion of clinical trials and focus on this disease and the development of not only agents using really creative approaches to stop production of the offending amyloidogenic protein, whether it's daratumumab in AL amyloidosis or patisiran vutrisiran approved in ATTR amyloidosis, other stabilizers and silencers are in development. So it's quite exciting.

(33:35):

It'll be important for us to use imaging, as I mentioned before, to help us understand how these drugs are working at the myocardial level. Sure, the drugs improve survival, that's what we hope they'll show or they improve six-minute walk distance or how people feel. But we really need to understand how functionally they're improving the heart, how structurally are they improving the heart? Because that will be kind of the proof of how these drugs are actually working, at least in the case of the organ cardiac amyloidosis that's principally affected.

(34:03):

But I want to also point out that we really need to take a lot of the imaging approaches that we are doing now very well at single centers, standardize them and transform them into multi-center approaches and this is also touched upon by Dr. Masri a second ago.

(34:19):

Much of the data that's been published in imaging in echo and MR in particular and also in nuclear scintigraphy has been single center studies with expertise. And there are a lot of vendors and there's a fair amount of confusion, I think around what techniques, specific techniques to use. So standardization of techniques, particularly in the world of MR, I think could be helpful. Or even echo though, there are different ways to calculate global strain, different techniques so that standardization will be important. And also the demonstration of the efficacy of these approaches in their capacity to actually determine change and associate that change with something clinically meaningful would be important to show across different sites so that we will rely upon standardization so that those tests can actually be used, take care of an individual patient and inform actual clinical decisions in the future, not just clinical trial results.

(35:09):

So I think that there's a fair amount of work to do in imaging and we're very excited to be doing it. But I do think that the imaging is really indispensable to the management of these patients that we treat with AL or ATTR amyloidosis, and will continue to be for the foreseeable future.

Dr. Renee Bullock-Palmer (35:22):

Great. Thank you so much for sharing your expanse with us today. So as we close, let's review the takeaways from today's discussion. So, Dr. Masri, if there is one or two things that you'd want people or listeners to remember about today's discussion, what would those be?

Dr. Ahmad Masri (35:34):

Well, I always use this opportunity to give two takeaways that not necessarily are related to the specifics of today, but one is always work up LVH. We have a lot of imaging tools at our dispense, so always work up LVH, consider it a significant structural heart disease. So don't just like hand wave at LVH. No, work it up. And then the second one is stay humble. There are many unusual scenarios and cases in amyloidosis or in LVH, and none of our imaging tools are a hundred percent specific or sensitive. So one has to keep an open mind to avoid misdiagnosis and mistreatment for patients.

Dr. Renee Bullock-Palmer (36:07):

Great. And Dr. Ruberg, what about you? What are your key takeaways?

Dr. Frederick Ruberg (36:10):

Thanks, Renee. I just wanted to thank you and such a pleasure working with such esteemed colleagues on this. So I completely agree with Dr. Masri's points and kind of a corollary to his points of staying humble is don't get tracked into one diagnosis. I always tell our trainees that just because you think you know about something, that something's happening with one particular person. The scenarios change and ATTR is a perfect example of a disease that typically occurs on top of other diseases. Someone may have had hypertension or may have had aortic stenosis, but then they subsequently developed ATTR amyloidosis. And so it becomes important to recognize that so that effective therapy can be brought to that patient. So people have to be vigilant, clinicians have to be vigilant and order the appropriate tests and recognize when the clinical scenario changes.

(36:53):

The second thing is that we in imaging are at a very unique position where we can connect dots. We can see the imaging. We can see the patient, and we can put other organ systems together and other clinical features together in a way that maybe other clinicians can't. And I say that simply because we have the capacity to look at the imaging ourself and understand potentially physiology or ultrastructure that we're seeing and connect that. So I think particularly in the world of cardiac imaging, we need to be vigilant. We need to think about what's happening with the entire patient and connect these clinical dots of say, carpal tunnel syndrome or spinal stenosis or proteinuria or peripheral neuropathy and or a family history. And then put that together with what you're seeing about the patient in front of you.

Dr. Renee Bullock-Palmer (37:38):

Wonderful. So this concludes our discussions for today, and I'm Dr. Renee Bullock-Palmer with Dr. Ahmad Masri, Dr. Frederick Ruberg and thank you for joining us today. So please also note that there will be a total of six podcasts on this topic that will be completed now through to June of 2023. And we hope that you can join us for the remainder of this series called ATTR: Closing the Knowledge Gaps in Transthyretin Cardiomyopathy. Please join us for the next podcast, which will cover treatment options including pharmacotherapy for TTR amyloid. Have a great day.