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Overcoming Challenges in Transthyretin Cardiac Amyloidosis

Announcer:
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Dr. Griffin:
Good afternoon, everyone. Thank you, Dr. Maurer. So let me see if I can figure this out. I can.

Here are my disclosures.

So these are our learning objectives for the next 15 minutes. We're going to discuss the etiology of ATTR and AL cardiomyopathy. We're going to highlight some of the clinical features that should raise clinical suspicion for the diagnosis, and then review a diagnostic pathway for the diagnosis of ATTR and AL cardiac amyloidosis.

So there are over 40 known amyloidogenic proteins. Over 95% of cardiac amyloidosis arises from either light chain, or AL, or transthyretin, ATTR, amyloid deposition. If it is deposited in the myocardium, it leads to a restrictive cardiomyopathy and in the nerves, sensory, motor, and autonomic neuropathy. But as you can see from the figure on the right, amyloid can essentially deposit it in any organ. Amyloid forms when a protein fails to acquire or loses its physiologic functional fold. This can occur because of post-translational modifications like oxidation, glycation, phosphorylation. It can happen due to abnormal proteolysis or due to point mutations in the gene.

TTR, transthyretin, is a homotetramer. It's made in the liver, and its main function is to carry vitamin A and also thyroid hormone. Due to the process of aging or due to inherited genetic mutations, this homotetramer can become unstable. It dissociates into monomers and oligomers, which then misfold and aggregate into amyloid fibrils. And these fibrils then are deposited for TTR mainly in the heart and the peripheral nervous system.

Light chain amyloidosis is a little different. It occurs due to the overgrowth of clonal plasma cells in the bone marrow, and these plasma cells then, in turn, produce an abundance of immunoglobulin-like chains, mainly lambda and also kappa. These light chains again are unstable, and they misfold, and in a similar manner form amyloid fibrils, which are essentially can be deposited anywhere in the body.

Cardiac involvement in patients with systemic AL amyloidosis occurs in about 60 to 70% of patients, and really is a medical emergency.

So the etiology of ATTR, the cause of wild-type is unknown. It's thought to be related to the aging process. A single amino acid substitution in the TTR gene leads to variant, also called hereditary or familial ATTR, and there are over 140 known pathogenic TTR mutations, which can result in variable phenotypic presentations. Wild-type TTR is the most common cause of cardiac amyloidosis in the United States, and the presentation of variant TTR depends on the actual genotype involved.

As you can see here, it can have a predominantly neuropathic phenotype, cardiac phenotype, or it can be a mixed phenotype. V122I is the most common variant in the United States and is found in 3.5% of Black Americans with a variable or unknown, unclear penetrance.

V30M is the most common variant worldwide. Early onset V30M presents at a young age, often in the 20s, more commonly found in Portugal or in those of Portuguese descent, and can cause a very debilitating polyneuropathy. Late onset V30M presents more as a mixed phenotype. And then T6DA originates from the north of Ireland, from the area of Donegal, and is present in around 1% of patients of Irish descent.

So amyloid, as I'm sure you know, can present with pretty non-specific features, and often these features just resemble those of more common age-related cardiac conditions. This is a table from the recently published ACC Concise Clinical Guidelines for ATTR Cardiomyopathy, and as you can see here, the cardiac manifestations, heart failure symptoms, family history of heart failure, conduction disease, AFib. Again, very non-specific features. Extra cardiac manifestations, carpal tunnel syndrome, spinal stenosis, these are all things you need to think about and ask about. About 80% of patients with cardiac amyloidosis have preceding orthopedic interventions, so hip or knee replacements, trigger finger release, biceps tendon rupture, which is typically spontaneous. TTR deposition has been found in the ligamentum flavum of up to 33% of older patients undergoing surgery. Spontaneous biceps tendon rupture can occur at a median of 5 years prior to the diagnosis of heart failure and carpal tunnel syndrome, typically bilateral, can occur 5 to 10 years prior to the diagnosis of ATTR cardiomyopathy.

So ATTR, specifically wild-type ATTR cardiac amyloidosis, was reported in 13% of patients with HFpEF and an LV wall thickness of greater than 12 mm in a group of patients hospitalized for heart failure. It was found in 16% of patients with severe calcific aortic stenosis undergoing TAVR, 5% among patients who had presumed diagnosis of hypertrophic cardiomyopathy, and TTR amyloid deposits have been found in autopsy in over 30% of patients with HFpEF over 75 years of age. Now, this is not a diagnosis of TTR amyloidosis, but actual just deposits.

So, you have to have a pretty high level of suspicion if you're going to think about diagnosing ATTR or AL cardiac amyloidosis. And the first thing people often think about is an ECG. They think about low voltage, but low voltage is not a very sensitive marker. It's only found in about 25 to 40% of patients with cardiac amyloidosis. A more sensitive marker is voltage to mass ratio, and this can help differentiate between cardiac amyloidosis and patients with other causes of increased LV wall thickness, like hypertensive heart disease or hypertrophic cardiomyopathy. Atrial fibrillation and flutter is pretty common, particularly in patients with TTR wild-type. It can be found in about 50% of patients. Conduction delay is always something to look for. Typically, looking for first-degree AV block is very commonly found in these patients, and a pseudo infarct pattern in patients who you know don't have coronary artery disease.

Echocardiography should be the initial screening test of choice if you suspect cardiac amyloidosis, but it is insufficient as an independent diagnostic test, and it cannot differentiate between AL and TTR cardiac amyloid. High-yield echo findings you see here on this slide, and just to touch on a few of them, to look for again increased LV wall thickness of at least 12 mm. You'll often see interatrial septal thickening and RV hypertrophy. The amyloid is deposited everywhere in the heart, so you're going to have increased biventricular wall thickness. You'll typically see a diffuse valve thickening. You may see a pericardial effusion and biatrial enlargement. On Doppler imaging, you may see the 555 sign, which is reduced tissue Doppler S prime, E prime, and A prime velocities. You're looking for restrictive transmitral mitral Doppler filling and elevated filling pressures in these patients.

And other imaging factors to look for, you may want to do longitudinal strain imaging, so speckle tracking imaging. You may find the apical sparing pattern on 2D speckle tracking imaging, and this this cherry on top appearance. And if you're looking for aortic stenosis, these patients often have a low-flow, low-gradient, severe aortic stenosis.

This is a very characteristic echo of a patient with amyloid. Here again, you see biventricular wall thickening, a very large left atrium. It's almost as big as the left ventricle, interatrial septal thickening, and this pericardial effusion is also present. And this is just an image of the cherry on top or apical sparing pattern that you can see in cardiac amyloidosis.

I'm not going to spend much time on cardiac MRI because Dr. Ruberg is going to speak later on it, and I certainly don't know nearly as much as he does. But just a couple of points to note is that interstitial expansion occurs due to the deposition of amyloid in the myocardium, and this avidly retains gadolinium contrast. You will often see in these patients global transmural or diffuse subendocardial late gadolinium enhancement, and this can detect disease before you see very obvious left ventricular wall thickening. Native T1 mapping can help identify amyloid deposition, and it has typically markedly increased in this patient population. And extracellular volume, or ECV, measurement can help to identify those at risk for amyloid deposition. And an ECV of greater than or equal to 40% is very characteristic of cardiac amyloid deposition.

So there are a bunch of algorithms which have been published, and typically I would just say find one that you understand and you can follow and stick to it. This one I like because I think it's pretty clear and straightforward, and it was again published in the ACC Concise Clinical Guidelines from earlier this year. So you're going to go into this obviously with some suspicion for cardiac amyloidosis based on your history, your ECG that we've talked about, and your imaging, whether it be echo, cardiac MRI. And the first thing you have to do is

rule out AL amyloidosis. That is always the first thing because if you miss that, it can be fatal very, very quickly. Median survival of 4 to 6 months in patients with advanced heart failure who are untreated or undiagnosed.

So, in order to rule out this AL amyloidosis, you need to send three tests. You send urine immunofixation with electrophoresis, serum immunofixation with electrophoresis, and free and serum-free light chains. And so, you want to make sure that these patients do not have a monoclonal protein and that they have a normal free light chain ratio. And I just want to draw your attention here to the right-hand side. In patients who have chronic kidney disease or renal dysfunction, there are reference ranges proposed for the free light chain ratio, which are a little different to the normal free light chain ratio, and this is because kappa and lambda light chains are filtered by the glomeruli, and as renal function worsens, these kappa and lambda light chains are filtered differently.

So again, just want to stress has to be serum and urine immunofixation electrophoresis that you send, and if you send all three tests, you have a 99% sensitivity for detecting AL amyloidosis. If you only send serum electrophoresis or urine electrophoresis with your free light chains, you could miss about 30% or up to 30% of patients with AL amyloidosis because you may miss the monoclonal protein.

So hopefully, at this point, you have ruled out AL amyloidosis. You have no monoclonal protein. You have a normal free light chain ratio. So the next step is to follow the pathway for the non-invasive diagnosis of ATTR cardiac amyloid, and to do this, you're going to perform bone scintigraphy, and you're looking for grade 2 or grade 3 uptake. There are three radiotracers which are available. The one we more commonly see in the United States is PYP, and in Europe DPD and HMDP. You have to perform, in addition to planar imaging, SPECT or SPECT/CT imaging, in order to ensure that you have a true positive test.

If you have no monoclonal protein on immunofixation, and if you have a normal free light chain analysis with a grade 2 or 3 scan, you have 100% positive predictive value for the diagnosis of ATTR cardiac amyloid, and you do not need to perform an endomyocardial biopsy. You have to remember, though, that grade 1 uptake can be seen with other subtypes of amyloid and other false positive diagnostic tests, which we're going to go through on a slide later on.

This on the top is an image, a planar image, which you will see with your bone scintigraphy scan. And this would be grade 3. It's very, very clear that there's uptake. But to ensure that the uptake is in the heart and it's not blood pool, you see on the bottom panel SPECT/CT imaging, and you can clearly see here that the uptake of the tracer is within the myocardium and not within the blood. So that's a grade 3 scan.

And so, not to belabor the point, but in order to perform the non-biopsy diagnosis for a TTR cardiac amyloid, you have to have a patient with unexplained heart failure or a pathogenic TTR mutation, imaging findings suggestive of amyloidosis, grade 2 or 3 uptake on scintigraphy, and you have to have ruled out AL amyloidosis. If any of these are missing, you have to perform a biopsy.

So, where do you biopsy? Well, you can see here on the right that extracardiac biopsy sites and subtypes of amyloidosis have different sensitivity for the detection of the amyloid or the amyloid protein. So, if you have a negative fat pad or a negative bone marrow biopsy, this does not rule out amyloid disease. And in that setting, you have to go for the clinically affected organ. So, typically, rather than, you know, wasting time in patients, if I'm worried that they have AL amyloidosis, I will go immediately for an endomyocardial biopsy if I suspect it's in their heart, rather than waiting for the results of a fat pad biopsy or a bone marrow biopsy, because you're wasting time on the diagnosis in those patients.

Some of the pitfalls that you can come across with bone scintigraphy. There are causes of false positive and false negative scans. Now, by including SPECT or SPECT/CT, you are improving the odds of having a correct diagnosis. But you may see a positive scan or something that looks positive in patients who've had a previous MI due to calcium deposition in the myocardium, and this is picked up by the tracer, and you do see this not too infrequently. As I've already mentioned, blood pool can lead to a false positive, particularly if you don't do SPECT or SPECT/CT. You could be easily fooled on planar imaging. Plaquenil toxicity, hydroxychloroquine, can cause a positive PYP scan or nuclear scintigraphy bone scan. And AL cardiac amyloid and other forms of amyloid can cause a positive bone scintigraphy scan. You can also get false negative scans. Some of the variants, like P64L, can cause a false negative cardiac bone scan, in early disease as well can appear negative.

Finally, just to briefly touch on the staging and prognostic tools which you may have seen in the literature, the Mayo and UK National Amyloidosis Center were the first two which were published. As you can see here, the Mayo utilizes troponin T and NT-proBNP, and the UK National Amyloidosis Center uses eGFR and NT-proBNP, and they provide you with stage 1, 2, or 3, depending on the thresholds for the biomarkers, and give you an approximate median survival for prognostication. The Columbia score, which was published in 2020 by Dr. Mauer and his colleagues, builds on these two previous staging systems by adding furosemide, daily furosemide equivalent, and NYHA class, and just provides additional prognostic discrimination upon the Mayo and the UK NAC score. You do have to remember, though, that the majority of these patients who were studied in these prognostic scores were not on TTR-targeted therapy at the time.

So, in summary, non-biopsy diagnosis of ATTR cardiac amyloidosis, you have to have grade 2 or 3 uptake, and you have to have ruled out the presence of AL amyloidosis. A negative fat pad or bone marrow biopsy does not rule out AL amyloidosis. AL cardiac amyloid is a medical emergency with a very poor survival if it is untreated or undiagnosed. You must ensure bone scintigraphy is not just performed with planar imaging but with SPECT or SPECT/CT. And always think about false positive or false negative nuclear scintigraphy. Thank you.

Dr. Maurer:
Fantastic. That was fantastic, and thank you very much. Okay, great.

These are my disclosures.

So, in general, just broad management strokes here. These patients have very high risk for atrial fibrillation, as you'll see. Anticoagulation, if you see AFib, is mandated irrespective of their CHADS-VASc score. Aortic stenosis, we talked about, can commonly occur with this particular condition. When it does, most of the time we do not advocate for a surgical intervention but a percutaneous intervention with a TAVR. Conduction disease is not uncommon, unfortunately; we survey for that over time. Many patients, about 20% in our practice, end up with a pacemaker, and we can talk why. But we often try to advocate for a CRT device because these individuals can become pacemaker dependent. They already have very low stroke volumes, and dyssynchrony is not a great idea. Ventricular arrhythmias are quite common in this particular condition. Unfortunately, or fortunately, they don't seem to have much prognostic significance, and we can chat in discussion about ICDs. But I think they have a pretty little minute role, and we spend a lot of time, obviously, managing the heart failure, which we'll talk about.

So, with regard to AFib, in most series it's at least 1/3 of patients, but in large trials it's been about 50-60% of patients. And my experience is over time, almost everyone with this disease develops atrial fibrillation. And again, you need to anticoagulate them. These are old data. I think we're all using, if you will, DOACs, not Coumadin, but you know, patients on Coumadin had times where they were falling out of the INR range, and they had more complications. But certainly, anticoagulation is really very important for these individuals.

The physiology is shown here. Dr. Griffin showed a slide, and you can see the ventricular chamber is smaller than the atrial chamber. This is a loss of ventricular capacitance, and so the end-diastolic pressure-volume relationship kind of shifts upward and to the left. The ventricle can't fill as well, and the difference between the, if you will, two vertical lines is decreased. So your stroke volume declines, and the body responds to that by basically augmenting salt and water retention and increasing the filling pressure and trying to normalize, if you will, the cardiac output. Notably, blood pressure in these patients still remains similar to what it was at baseline or lower than normal.

So, if you think about this, this progressive upward shift in the EDPVR and reduced ventricular capacitance, it's associated with a decline in one's stroke volume and therefore a decline in one's cardiac output, and therefore a decline in one's blood pressure. In fact, one of the clues to this disease is someone who was previously hypertensive, and you're pulling back medicines despite them having HFpEF, because the most common comorbidity in HFpEF is concomitant hypertension. So you see someone in the office, heart failure, preserved EF, and a normal blood pressure, think amyloid. And this is also a role I think for deprescribing. The geriatrician in me starts to come out and say, "Do they really need the beta blockers, ACE inhibitors, or ARBs or ARNI therapy when their blood pressure is so low?"

So the challenge I think in using goal-directed medical therapy or guideline-directed medical therapy in these patients is they have a very fixed stroke volume, they have concomitant conduction disease, autonomic dysfunction with fragility in their ability to main homeostasis and a decreased functional capacity. And so, at the end of the day, you know, many agents that we typically use in heart failure are not very well tolerated. And you'll see the data supports the use of SGLT2s and MRAs for patients, and maybe for select groups of patients, ACE inhibitors, ARBs, and beta blockers.

So these are data back to Richard Chang, who helped us develop the Columbia score, along with Wayne Levy from our data set. These are pretty advanced patients many years ago, but I think makes the point: beta blockers were not associated with a survival benefit, nor was ACE ARBs or ARNIs. And at the end of the day, what we noted we were removing beta blockers from patients. The removal here is shown in the bluish line. When we stopped the beta blocker, there was actually a much greater survival than in the patients who we continued the beta blocker on, and so this led to concerns about beta blockers. The most commonly used beta blocker in the study was carvedilol, and it was pretty high dose.

More complicating, but I think also more comprehensive data comes from the NAC. This is a large study of patients who they saw at their center, over 2,000 patients with TTR amyloid. ACE ARBs or ARNIs, again, not associated with any mortality benefit. Interestingly, beta blockers in this study, but it was mainly bisoprolol, and the average dose was 2.5 mg. So very low-dose beta blockers in those with an EF under 40 was associated in this data set propensity matched with better outcomes, and MRAs across the spectrum of ejection

fraction were beneficial as well.

There is a rationale in this disease to think about SGLT2 inhibitors, and that rationale comes from the idea shown here that the more diuretics someone takes, the worse they do. These patients have very high CVPs, they have low blood pressures, they develop a cardiorenal syndrome, and we know that SGLT2 inhibitors in larger studies in HFpEF in general are quite effective in preventing hospitalizations and preserving renal function.

So these are data again from our center looking at patients who were given an SGLT2 inhibitor and those who are not. And what I think you can see is that the diuretic dose actually went down in these particular patients by about a loop diuretic dose reduction about 25%, and paradoxically, their weight is also going down, such that they're losing weight, irrespective of you giving them less diuretics. There is a little bit of a drop in renal function, but it overall is maintained.

And these are supplemented, I think, by this very elegant study again from the NAC that was propensity matched, looking at about 200 to 250 patients who received an SGLT2 inhibitor with TTR amyloid, and a group of patients same phenotype, same age, renal function, and there were demonstrable benefits of these agents in this propensity-matched analysis, slowing the decline in renal function, reducing hospitalizations, reducing the rise in NT-proBNP, and even associated with a mortality benefit.

For pacemakers, I mentioned very high pacing requirement in these patients. When they do need a pacemaker, they almost all become pacemaker dependent. And these are data from Maz Hanna and his group at the Cleveland Clinic, demonstrating in patients who got CRT devices versus those who did not, that the CRT seems to be associated and again non-randomized cohort data suggesting CRT devices are really beneficial. I remind you that these patients have the lowest stroke volume of anyone with some heart failure in general, and so we try to preferentially, when we put a pacemaker in, put a CRT device in.

These are the consensus or concise clinical guidance updates that were distributed. Rick Ruberg, along with Michelle Kittleson and others, helped draft these. And I'll focus mainly on the green in the middle, demonstrating that for patients who have, you know, who are appropriate for disease-modifying therapy, which is the majority of patients, besides heart failure management, that people talk about, you know, what other agent, which of the different agents could be utilized, and the main message I would say is all the agents work and they're all effective, and the only bad choice is not to put someone on one of these agents. And this particular piece I think does emphasize that in patients who have variant disease with a concomitant neuropathy, silencer preferred by most of us, but for the vast majority of patients, any of the three agents are effective, and it's strongly recommended, at least at this point, against combining treatment options.

So, to review the pathophysiology of the disease, we've heard about several times, but this is a protein made by the liver, a tetramer, dissociates into oligomers or monomers that forms the amyloid fibrils. And in this review that Dr. Griffin, myself, Dr. Ruberg, and others drafted, there were strategies. The first was the stabilizer treatments which include tafamidis and acoramidis or off-label diflunisal. There is, if you will, gene silencing, either with gene editing, which is experimental, and I won't touch upon—it's still using CRISPR, but with agents like vutrisiran, patisiran, or eplontersen to knock down or silence TTR, and then the pie in the sky is the idea of amyloid removal with monoclonal antibodies that's under active investigation.

So tafamidis was the first kid on the block. This was the publication in 2018. This was the ATTR-ACT trial in which patients who received tafamidis either 20 or 80 mg, it was pooled versus placebo, had a significant clinical benefit. This was a hierarchical model that was used, comparing each patient on drug to patients not on drug, so-called win ratio. The most important part of the slide, though, is the absolute reduction in mortality was 13%, not relative risk reduction, but absolute, and that translated quite surprising to all of us because it was a small study in which we thought we were using this fancy statistical technique because we didn't think Kaplan-Meier curves would work into a clinical benefit, even in patients using Kaplan-Meier curves here, which, as you can see, a significant reduction in the risk of all-cause mortality. And that risk was even larger when we quote unquote removed the patients who rarely got a heart transplant in this or an LVAD. Again, the drug was highly effective at reducing the number of cardiovascular hospitalizations as well, with a number needed to treat of 4 to prevent 1 CV hospitalization in this cohort of pretty sick patients back in 2018.

We learned from this trial that earlier is better. So across all the pre-specified endpoints, everything looked very good in favor of active drug, except for the patients with NYHA class III. Those are patients who live longer with these agents, but actually live in a state in which they're at increased risk for cardiovascular hospitalizations, and I guess we could debate: is that the right approach, you know, for therapies.

So that message is conveyed here, which has come out in all the other trials, as I'll show you, in which in the rare patients that we found in this study, less than 10%, 37 patients out of 441 who were NYHA class I, while the confidence intervals are wide, the point estimate shows you that there is a marked reduction in mortality, 64% versus class II 39% versus class III much less. So the whole idea of all these therapies is find the patient as early as possible.

These are data from our center, where you can just see back in 2001 to 2013, the blue bar we had to biopsy everybody. Now we biopsy very few patients. You can see in gray the staging of advanced Columbia stage has become much less common, and we're using disease-modifying therapy much more frequently. And that's translated into dramatic improvements in outcomes that are mediated not just by drug administration but by everyone finding people earlier. So survival has gone from a median of 2.5 years to now a median that's not even reached at 5 years, and my estimate is somewhere around 7-year survival for most patients, and potentially greater for people with earlier disease.

The next kid on the block was acoramidis, another TTR stabilizer. This is data from the ATTRibute-CM trial published in *The New England Journal*. This is an agent that mimics the T119M super stabilizing variant. They used a hierarchical endpoint that involved, if you will, four components. But you can look at the bottom, similar to the ATTR-ACT trial, death from any cause and CV hospitalizations, the win ratio was markedly in favor of this agent. And interestingly, we learned later on that serum TTR levels increase with stabilizers, and they go down with silencers. And this has become an emerging area of active research in biomarkers.

The trial itself, and these are the Kaplan-Meier curves, showed no statistically significant during the trial benefit on mortality. Having said all that, these were much healthier patients, and so much lower event rate for mortality. And you'll see in a minute, longer-term follow-up does show that the drug has, I think, a significant effect on mortality. It did have a huge effect on cardiovascular hospitalizations. And with morbidity, there were a slowing of the decline in 6-minute walk and KCCQ, like was seen in the ATTR-ACT trial.

These are the longer-term data published by Dan Judge in follow-up, and you can see here mortality and mortality in cardiovascular hospitalizations with a 50% reduction in the latter when this agent is prescribed upfront. So very effective.

And these are provocative data that were just recently published, in which this agent is associated with a slight decline in your eGFR, similar to what we sometimes see with ACE, ARBs, or ARNI. And then you can see in blue the slope of the line of the eGFR over time with acoramidis versus placebo, seemingly having potentially some clinical effects on stabilizing renal function over time, which is also seen in the open-label extension, where when patients were switched in orange to active drug, there's a drop in the eGFR, but the slope of the decline seems to stabilize. Somewhat provocative.

With regard to the second approach, not stabilization but silencing, there are different ways to do this. You can use siRNA with vutrisiran, antisense with eplontersen, or as I said, potentially in the future, if effective gene editing, which is under study with CRISPR-Cas9. So this is the HELIOS-B trial published, you know, 2025 in *The New England Journal*, run by Marianna Fontana and others, and this was a trial that again led to demonstrable endpoints—demonstrable benefits, I should say—in multiple endpoints in the trial, including the primary, which we always look at as composite of CV events and all-cause mortality, and multiple secondary endpoints, including quality of life, functional capacity, and New York Heart class.

Here's the data, again I think similar to previous showing in the overall population that is in patients who were on both vutrisiran and tafamidis, about 40% of the patients in this trial were on tafamidis therapy, and in those who were on so-called monotherapy, those patients who were not receiving tafamidis at baseline. And an additional about 20% of patients dropped in on tafamidis during the trial.

Again, this is the signal that I think is important for everyone to understand. If you look at different subgroups, looking at either all-cause mortality, recurrent events on the left, or all-cause mortality, and you look at the hazard ratios, in particular, using, for example, NT-proBNP above or below 2,000, you can see that there's greater benefit with a lower hazard ratio in general in patients who have earlier stage disease. So again, main message: try to find the patient as early as possible with this condition and institute therapy as early as possible.

And this agent also seems to have some effect that's being promulgated and shown here with regards to declines in eGFR, in which there are much less declines in the eGFR. In this case, using a 40% cut point in those who were assigned to active therapy versus placebo.

So, with now three available agents, there are a whole host of questions that have come that I don't have easy answers to, I assure you. Which therapy should you pick? Should you ever switch from one to another? Should you ever stop therapy? Should you combine them? And so forth. There's huge financial burdens to some patients with regards to these therapies, and we don't have really good head-to-head data to guide outcomes.

These are our attempts. My colleagues and I, a while ago in this paper that I pointed in *JACC: Heart Failure*, looking at the various trials, and I think you should realize that they're potentially not easy to compare, mainly because they were conducted in different time periods. And just look at the row of placebo mortality; it has plummeted, right? And CV event rate has plummeted. And why is that? That's because you guys are doing a great job at identifying people earlier with earlier New York Heart class and lower NT-proBNPs. So that idea is shown here in a curve that Brett Sperry put out, which I think is very elegant, looking at the placebo groups. And you can see

that there are improvements in mortality even in the placebo arms, and that's because the lower stage disease. But every agent on top of the placebo arm improves outcomes.

And these are the point estimates and the 95% confidence intervals with regard to the various agents regarding their primary endpoints, mortality, CV events, and then the key secondaries. And my read on all of this is that they're all very effective with wide confidence intervals and overlapping, so you really can't at this point I think conclude that one agent is markedly superior to another.

The latest trial is CARDIO-TTRansform. This is a trial of 1,432 patients in ATTR-CM using eplontersen, a subQ silencer given once a month, and was the largest trial conducted so far to date, including both wild-type and variant patients. The primary endpoint in this trial was slightly different. It was both CV mortality, not all-cause mortality, and clinical events up to a set time period of 140 weeks. There were similar secondary endpoints that were pre-specified with regard to function in KCCQ, and lots of exploratory endpoints with regard to imaging.

We've presented the baseline characteristics of this study. I think pretty similar to what we've seen in other trials. Average age is 77, predominantly males at 90%, predominantly wild-type patients, and mainly NYHA class II, and a majority of patients are UK NAC stage I on the usual medical therapy with KCCQs of about 73 and 6-minute hall walks of 35.

And just to highlight some of these baseline characteristics as the largest trial, again predominantly males, predominantly older adults and predominantly wild-type, but there was a wide spectrum of disease in this particular trial, including patients with NYHA class III, even NAC stage III, with NT-proBNPs, with no upper limit in some regard. Probably most importantly in this trial was that 57% of the patients at baseline were on a TTR stabilizer that's become standard of care, and an additional large percentage of patients dropped in on stabilizers. And SGLT2 use at baseline, which is becoming more common, was common here and increased quite a bit during the course of the trial.

And probably both of those led to this, which is the study was announced just recently, and it missed its primary endpoint, trying to reduce CV events and CV mortality. And notably, there was a pre-specified subgroup. Can't talk about specific p-values, but nominally significant in the patients who received eplontersen monotherapy, and there was a favorable safety profile. So results of this trial will be reported more comprehensively, I think, at ESC, and we'll learn quite a bit. I do believe these results will be important in practice-changing.

So I'll summarize by just saying we've gone from a disease that was rare and underdiagnosed to one that I think everyone is seeing in their clinical practice, and one that had essentially no therapies to one that has a plethora of treatment options. We have two TTR stabilizers, including one acoramidis that I mentioned earlier today, is being studied in allele carriers in the ACT-EARLY trial. We have patisiran and vutrisiran silencers. We have a next-generation agent called nucresiran, which is dosed every 6 months that's now in a trial called TRITON-CM and PM, and actively recruiting. We have next-generation silencing with CRISPR-Cas9, a single IV infusion, and then the whole arena of monoclonal antibodies, with the hope that, you know, in those hopefully less commonly seen lately, but advanced patients who have a boatload of amyloid in their heart, we might be able to reverse, remodel the ventricle, and remove amyloid. So that'll be determined by upcoming and currently being performed phase 3 clinical trials. I would still encourage everyone try to dose the patient earlier and not wait for clinical consequences.

So I will turn it over now to my esteemed colleague.

Oh, sorry. Just the practical tips: stabilizers make the protein go up, silencers make it go down. It's one way to measure efficacy. And don't forget, in patients who are taking a silencer, they have to be on a vitamin A supplement because you've removed the protein that can transport vitamin A. You don't want them to develop any consequences of vitamin A deficiency.

So, I'm going to turn it over to my esteemed colleague Rick Ruberg. He's the Chief of Cardiology at Boston Medical Center. We've had collaborations for years, and he's going to talk about individualized patient management with a case, and then we can open it up for questions. Thanks again for your time and attention.

Dr. Ruberg:
Thanks so much, Matt and Jan, and thank you for staying. And it's such a pleasure to follow such clear and concise presentations. And I'll reiterate a lot of points.

Now, spoiler alert: the answer to this case is ATTR cardiac amyloidosis, and you can all now leave now because you know the answer. But the key is not like how you get there, because I'm going to go over that, which really reiterates what Jan talked about. It's more like about what are you going to do and how you're going to treat.

So here are my disclosures.

So this is a 68-year-old man whom I met on the inpatient cardiology service in my hospital from Cape Verde, and he presented—we'll show you where that is in just a second. Many of you may know where that is now after the World Cup—in 2023, I met him over the summer about 3 years ago, and he presented with heart failure and chest discomfort, abdominal fullness and dyspnea. And he said someone was pushing a finger on his chest, and his heart was racing, dyspnea on exertion, all the symptoms and signs that you're familiar with.

Now, we had some pretty unusual laboratory values with a markedly elevated high-sensitivity troponin I, which you can see there, which didn't rise and fall, but it was sustained at a very high level. His proBNP was elevated, his eGFR was normal, and he had no cardiovascular risk factors. And I just want to highlight where Cape Verde is. For those of you who know, it's an archipelago off the west coast of Africa, and obviously made it to the knockout stage this year in the World Cup for those of you who follow soccer. But its location actually is really important when we think about what type of amyloidosis this patient has. Some of you may already be kind of like doing the math.

Here's his ECG, pretty unremarkable sinus rhythm, not low voltage. So just like Dr. Griffin said, sure, if you see low voltage, that's helpful. But you know, sometimes you don't, and a lot of times you don't. In this case, ECG showed pretty much normal voltage. So he got an echocardiogram, of course, a standard of care, and he had a mildly dilated LV cavity with only mildly increased wall thickness and mild systolic dysfunction. But he had pretty pronounced diastolic dysfunction pattern with increased filling pressures, normal RV, no significant valve disease, and an estimated artery pressure of 8.

Now, I'm not going to torture you all with what the next step is because you're all thinking the guy had a troponin of 3,000. Obviously, I'm going to send him to angiography, and that's what happened. But he had no coronary artery disease, which is often also the case. Really like minimal coronary disease, certainly not explaining his LV dysfunction. So, how do we approach this? This patient has a situation called MINOCA. He's got a myocardial injury pattern, but no coronary artery disease. And these are data that were recently published by Harmony Reynolds, basically showing that the approach to this in 2026 is a combination of invasive angiography with OCT, if you could do that, and cardiac MRI.

So the patient got a cardiac MRI, and this is his cine cardiac MRI. And Jan alluded a little bit to this. So these are cine images, which really are like, you know, don't really tell you that much more than the echo tells you, and except that the spatial resolution is outstanding, and the heart function is mildly reduced, and the wall thickness is mildly increased, and he had really kind of biventricular mild dysfunction.

Now, this is actually something I'm not going to ask everybody to interpret, but this is something called a Look-Locker sequence that we do in cardiac MRI, and it shows this characteristic pattern where the blood and the myocardium null at the same time, which usually results in LGE images that look like this. Again, Dr. Griffin showed you that late enhancement is one of the key ways we look at amyloid. Unfortunately, a lot of times in amyloid, late enhancement images look like trash, like this. Terrible image quality. You can't even tell where the heart is, and that's because the blood pool and the myocardium are so similar in their signal characteristics.

But he had diffuse late enhancement. And again, Dr. Griffin alluded to this as well. The native myocardial T1 was markedly elevated, and the post-contrast myocardial T1 shows that the blood pool and the myocardium was basically the same, which really means that there's just a diffuse expansion of intracellular space. That's because it's amyloid; it's increasing the space between cells. Contrast accumulates, and the ECV in this case is 53%. And as Dr. Griffin showed you, anything more than 40% should make the MRI reader like me think about amyloidosis.

And this is just a nice review by Marianna Fontana showing how we've evolved in our thinking of MRI and cardiac amyloidosis over the past decade. It really has become kind of like the gatekeeping test for wall-thickening diseases certainly in younger people, and you can make an argument in older person to go to PYP imaging if you think about amyloid.

So again, just to not to belabor the point, Dr. Griffin mentioned first you check for a monoclonal protein. You can see here that his free lambda and free kappa were in the normal range because the ratio is normal, and his immunofixation was normal, and his kidney function was normal. So we've excluded a monoclonal protein. Yes, 1% of these people could have AL amyloidosis, but in this case, I think the thinking was not likely to be so.

So we proceeded to scintigraphy, and again, as Dr. Griffin showed you, this is again a real case. You can see the planar image on the right showing diffuse grade 3 uptake, much more than bone, and the SPECT/CT imaging showing myocardial and not tracer uptake, again demonstrating cardiac amyloidosis. So this patient has ATTR cardiac amyloidosis because he had no monoclonal protein, and he had diagnostic imaging indicative of amyloidosis. And in that context, as we have shown well now 10 years ago, you can make the diagnosis without tissue biopsy.

The next step is going to be genetic testing, and that's what happened for this patient. Now, his prealbumin was very low, only 17. We'll talk about that in just a second, and he had this variant that Dr. Griffin mentioned called V142I. So this patient has hereditary V142I cardiac amyloidosis. And the V142I variant originated in West Africa. And as I showed you, Cape Verde is just off the coast of West Africa, so you could imagine that there potentially could be some migration back and forth.

This V142I is a very important variant because there is many people in the US, over 1.5 million who carry it. There's almost 0.5 million people who are over 50 who carry it, and they've been, you know, by epidemiologic modeling, proposed to lose a substantial amount of life. But the important thing is it doesn't interfere, obviously, because with someone's capacity to pass it on. So this patient had 16 children from 14 different mothers. This is true. I did not make it up. So I'm asking Dr. Maurer, who's given a lot of thought to cascade testing. How do we approach this scenario? And you can talk about.

Dr. Maurer:
I think he needs to learn his actions have consequences first and foremost. But yeah, no. I mean, this is a huge problem. I mean, we all talk about, and I think it was Barry Greenberg showed data that, you know, genetic testing is, you know, underutilized. But this is just to comment, a gene that doesn't have any real big variants of unknown significance. It's very straightforward, and we know a lot about early prevention. So, I think this is a failure of implementation. I don't know how to fix this problem, but it's something that in healthcare we need to do a lot better at, which is trying to communicate to individuals that this risk is real, that it's really important for their kids to get early tested. As we said, we have trials now potentially trying to prevent the development of disease, but it's going to be complicated by lack of trust potentially where the kids are all over the country, different providers, and it's not a simple thing to solve. Rick and I have written a few grants that have been unsuccessful in this arena trying to tackle this. But.

Dr. Ruberg:
Yeah, and just statistically speaking, since a 50% chance of passage, 8 of his children will have the V142I as well, and probably not know it unless we do our best to identify them.

Okay, so we've already gone over this. Jan already showed this slide. This is a nice review that Matt wrote a number of years ago about the clinical importance of this. So let's talk about treatment. So Jan, I'm going to show a figure. It's a beautiful figure from your paper. How do you approach treating this guy with V142I TTR?

Dr. Griffin:
Okay, so well, the first thing I want to know is, does he have any neuropathic symptoms? Has he seen a neurologist?

Dr. Ruberg:
Important question. Super important question. The answer is no. V142I, not commonly associated, but you know, there may be a signal there, but for this patient, no neuropathy.

Dr. Griffin:
None. Okay, so I suppose most of the data for neuropathy is with silencers. If he had any signs of neuropathy, I would probably steer him towards a silencer. In this case, either vutrisiran or eplontersen, which is both being approved for ATTR with polyneuropathy, with or without cardiomyopathy.

Otherwise, you know, I think it's very much down to a discussion that I will have with my patients. Do you want a pill? Do you want an injection? Some people are very opposed to injections. I totally get it, but others would rather have, you know, either a once monthly or a once every 3 months subcutaneous injection. And if that's the case, wonderful. They'll all get their vitamin A and will steer along the avenue of injections. If they don't want an injection, if they just want a pill, then I will, you know, I'll propose the two tablet formations with them, discuss potential side effects, and then it's really unfortunately up to the patient due to the lack of head-to-head data between all of these drugs, right?

Dr. Ruberg:
Right. I agree. That's exactly my approach. Matt, would you agree with that too?

Dr. Maurer:
Yeah, yeah, I'd do the exact same thing. I think someone mentioned it before. I think it was Anjali related to HCM. Sometimes you don't get to choose as the provider because their insurance chooses for you. So the key message here is you need treatment. We don't want you to not go with treatment, but we have three good options. If you have a preference, we'll try to get it. But if we can't get your preference, you should still take one of the other agents that your insurer is paring with through your insurance.

Dr. Ruberg:
Exactly. Exactly. And we'll get to the issue of when to switch and when to not a little further on.

So this was 2023, and there was only one approved drug, so he did get tafamidis. Okay, but here's what happened to his TTR. So, Matt, you alluded to prealbumin raise with acoramidis. So this is tafamidis. So what can you infer by this? And yeah, would it have any meaning for you in terms of whether the drug is working or not, when you should switch? What do you think?

Dr. Maurer:
Yeah, I mean, this is a class effect. Both stabilizers raise serum TTR levels. I find it a nice way to say to a patient the drug's working in the office to show them that their TTR levels go up, because these drugs don't usually have any side effects, and some patients are a little suspicious as to whether it's actually working. You know, and we've shown on a population level that increases in serum TTR seem to be associated with better prognosis with regard to all-cause mortality and now even other clinical events. I don't personally use this to make any clinical decisions in the office on an individual patient with regards to this.

And the truth is, a vast, vast, vast majority of patients, meaning 199 out of 200, have an increase in their serum TTR. I've seen one or two patients with a stabilizer who don't, and in that circumstance, I actually was worried about the patient. They usually have very weird variants, and I actually chose to, when available, use a silencer just because of efficacy issues, but that's not very common.

Dr. Ruberg:
Alright. So, Jan, what else would you add? So, we put this patient on tafamidis because that's what we had. Would you add anything else to his regimen? How would you treat?

Dr. Griffin:
Oh, yes, I would. So, apart from, you know, targeting the TTR, like Dr. Maurer mentioned and reviewed heart failure therapies. So, firstly, you know, they may or may not need a loop diuretic. There are some of my patients who don't need a loop diuretic. If they do, I'm going to go for something like Bumex, it's more bioavailable than furosemide. But also, SGLT2 inhibitors, mineralocorticoid receptor antagonists. I try to get them on, all my patients, as long as there's no contraindications.

And in addition, deprescribing. So I don't want them to be, you know, if they do have a reduced EF, I don't need them all on an ARNI. It's going to probably make them very hypotensive and make them feel absolutely terrible. I'm not trying to drive their blood pressure down and afterload reduce these people. They're very different to your regular dilated cardiomyopathies. Beta blockers, as Matt mentioned, you know, they can make people feel absolutely terrible, and it can make them sicker. So, in addition to adding, you have to think about what you can remove from their med list.

Dr. Ruberg:
Exactly. So, and this is a slide that Matt's already shown, just kind of mirroring Jan's points, among the data that support the use of SGLT2 inhibitors and MRAs in this population, which has pretty much become, I wouldn't say standard of care because there isn't really a standard of care, but I think most of us are doing it. So that's pretty much how we approach it. And as Jan said, we avoid ARNI, even though this guy's LVEF was in the low 40s. His blood pressure was normal. He did not require a loop diuretic, so that's how we managed him.

So, Matt, how do you know whether the drug is working? This is a recent publication in *JACC: Heart Failure* from Pablo, and I think you may have been part of that paper. So what tests do we order? What assessments do we do to determine whether or not patients are getting better or worse?

Dr. Maurer:
Yeah, I mean, so this has become a whole hot area of disease progression. This paper highlights some of the things we utilize. Obviously, we talk to patients. You can rate their NYHA class. I personally think heart failure-related hospitalizations are not a progression criteria but an outcome that we're trying to prevent. So I lost in that battle in this document, but it's okay.

Increases in oral diuretics, like loop diuretics, is a bad thing, and as we saw, is associated with worse prognosis. That's called outpatient worsening heart failure, or people call it oral diuretic intensification. And your natriuretic peptides can go up. There's a 700 pg/mL and 30% from baseline is considered progression, a drop in your eGFR, and then functional capacity and quality of life.

The main messages from this, I would say, are a fewfold. A, one criteria here does not meet progression criteria. Patients need to have two or more. Many people will have one of these, and some of them can occur in background of dietary indiscretion. Your NT-proBNP goes up, you adjust their diuretics, it comes back down, and it wasn't really, you know, a set criteria. And then the other thing is, unfortunately, patients progress, but there's absolutely no evidence that changing or adding disease-modifying therapy is actually going to ameliorate that progression. I understand that's logical for all of us to want to do something, but progression, in my experience, in most cases is actually mediated by the underlying heart failure and their amyloid, and not TTR biology. And so, throwing more drugs or switching drugs is probably, in my experience, not a great idea. If you're going to do it, I think you better at least come clean and tell the

patient I'm doing this. I'm not sure it's going to work, so that they are all comfortable at the end. If it doesn't work, that you don't have like egg on your face and promising them something that didn't happen.

Dr. Ruberg:
I think it's super. Thank you for that overview and from the kind of the inside baseball look at how you put this together. But I also think you made a super important point about that ATTR disease progression or change in these variables necessarily reflect progression of ATTR amyloid. It could just be the heart failure or the other, you know, company that it keeps essentially for these patients. Many of them, sometimes they have fibrosis as well, especially if they have advanced disease, and so it could just be non-amyloid.

Okay, so I'm going to skip through this in the interest of time because it's already been shown. I think Matt showed this, and Matt also went through some of the unanswered questions. Jan talked about this a little bit in her comments. What's the best therapy? And you know, Matt addressed a little bit about combining therapy, and maybe that'll come out a little bit and as we learn more over the summer with CARDIO-TTRansform. Disease progression we talked about. We didn't talk about disease prevention because it's not really applicable to this case. But we could answer it in the Q&A. And cost effectiveness is also an important point. And it really becomes individual for the patient.

So I'm going to close just by showing a few kind of provocative points. This patient's troponin really bothered me. Yeah. See, it's like around 3K and doesn't go anywhere, and I'm just worried that he's like slowly infarcting his heart. And the mechanism we're not going to talk about today, whether it has to do with like toxicity from amyloid fibrils or prefibrils, but I became interested in the concept of kind of chronic ischemia.

So I sent this patient to a rubidium perfusion flow reserve analysis, which demonstrated pretty marked flow reserve in all three. And many of you are using this monitoring for transplant vasculopathy. And this patient obviously had normal epicardial coronary, as we know from angiography. So he has markedly impaired coronary flow indicative of diffuse microvascular disease, which is probably causing some degree of ongoing ischemia, and this has been studied in a couple of studies. Two of them I reproduced here, which basically concluded that patients with ATTR or cardiac amyloidosis could have as bad flow reserve as somebody with three-vessel epicardial coronary disease. And you have to believe that's not good for people.

So I will ask my esteemed panelists this kind of the last question: What can we do about this, if anything? Jan?

Dr. Griffin:
What age is he again? Can I transplant him?

Dr. Ruberg:
He's in his early 60s.

Dr. Griffin:
Yeah. As a last resort, I can transplant.

Dr. Ruberg:
So yeah, yeah.

Dr. Griffin:
Otherwise, I'm not sure.

Dr. Maurer:
Yeah, I would agree. I think this is a huge problem and underrecognized. All the data suggests that they have really bad microvasculature. I don't know what to do for individual patients to ameliorate this. I have a patient right now who has got Thr60Ala, has an NT-proBNP of a few hundred, has an EF that's preserved. His walls are thick, and he actually had very uncharacteristically like VT storm, and got a few shocks. And they just cathed him to make sure he didn't have epicardial coronary disease. And the person who did it called me and said, "It sure looks like a transplanted heart," just like Rick was saying, where the tertiary branches are all pruned. So I think this guy, he actually has a GLS of, you know, maybe -6 or something. So, you know, quite poor, you know, strain, and I think at the end of the day this is a big bane of existence for patients.

Dr. Ruberg:
Yeah, I guess I think I would agree. There's not much we can do, and I don't think here symptomatic treatments really help very much, and I guess the key is to not let it get to that point.

So, just to follow up, my last slide. This patient actually has done really well on tafamidis, so you could argue that he has not achieved an outcome, as Matt said. He has been hospitalized for chest pain, and it's really required like an act of Congress to keep him getting

cathed again, which I think we have successfully done. However, because of the approval of silencers and his high troponin, and us being nervous, we did transition him to patisiran. And we could talk about why, or, you know, in the Q&A if you'd like. No data for this. His trop remains really high, but his proBNP actually came down nicely with medical therapy, and his prealbumin is in the process of being suppressed. That's actually like a 3-month removement. His GLS remains stable. His EF remains stable, and yeah. And I'm not sure. We're hoping to reach his 16 children. So with that, I'll stop, and we'll take questions and move on. Thank you.

Dr. Maurer:
So I don't know if anyone has a question, you head to the mic. But I would just say I'm curious; so in patients who have relatively early disease that we're seeing nowadays, without a heart failure syndrome, say an NT-proBNP of 200, normal renal function, are you adding SGLT2s and MRAs to those patients who are New York Heart Association Class I? Either of you?

Dr. Ruberg:
Jan, you can start.

Dr. Maurer:
Yeah. So, no heart failure, amyloid diagnosed on disease-modifying therapy. Are you giving them an SGLT2 inhibitor?

Dr. Griffin:
I am. Yes.

Dr. Maurer:
You are.

Dr. Griffin:
Yeah.

Dr. Ruberg:
If they don't have any heart failure symptoms and their renal function is normal, I am not, yeah, but I'm more conservative.

Dr. Maurer:
I think the jury's out in that particular realm on, you know, how far to go, but most of the studies that we talked about, which are reasonably high quality, but obviously not randomized trials, do not include people who didn't clinically have heart failure. I'm debating it back and forth in my head, and depending upon the patient profile, I'm more often doing it than not. But I wouldn't say it's universal.

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