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Expert Perspectives on AL Amyloidosis: Timely Identification for Improved Outcomes CME

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Target Audience
This activity is intended for cardiologists, nephrologists, hematologists, primary care physicians, and nurses.

Goal Statement
The goal of this activity is to educate clinicians about amyloid light chain (AL) amyloidosis characteristics and the importance of coordinating timely care with the interprofessional team.

Learning Objectives
Upon completion of this activity, participants will:

Have increased knowledge regarding the
- The clinical presentation of AL amyloidosis
- Data for emerging and new therapies for the treatment of AL amyloidosis

Have greater competence related to
- The diagnostic evaluation of patients who present with symptoms consistent with AL amyloidosis

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Hardware/Software Requirements

To access activities, users will need:

- A computer with an Internet connection.
- Internet Explorer 8.x or higher, the latest versions of Firefox or Safari, or any other W3C standards compliant browser.
- Adobe Flash Player and/or an HTML5 capable browser may be required for video or audio playback.
- Occasionally other additional software may be required such as PowerPoint or Adobe Acrobat Reader.

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Received grants for clinical research from: Caelum/Alexion; Janssen
Anti-CD38 Antibodies for Treatment of Light Chain Amyloidosis and Other CD38-Positive Hematological Malignancies. Patent WO2016187546A1

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Received grants for clinical research from: Alnylam; Eidos; Ionis/Akcaea; Pfizer

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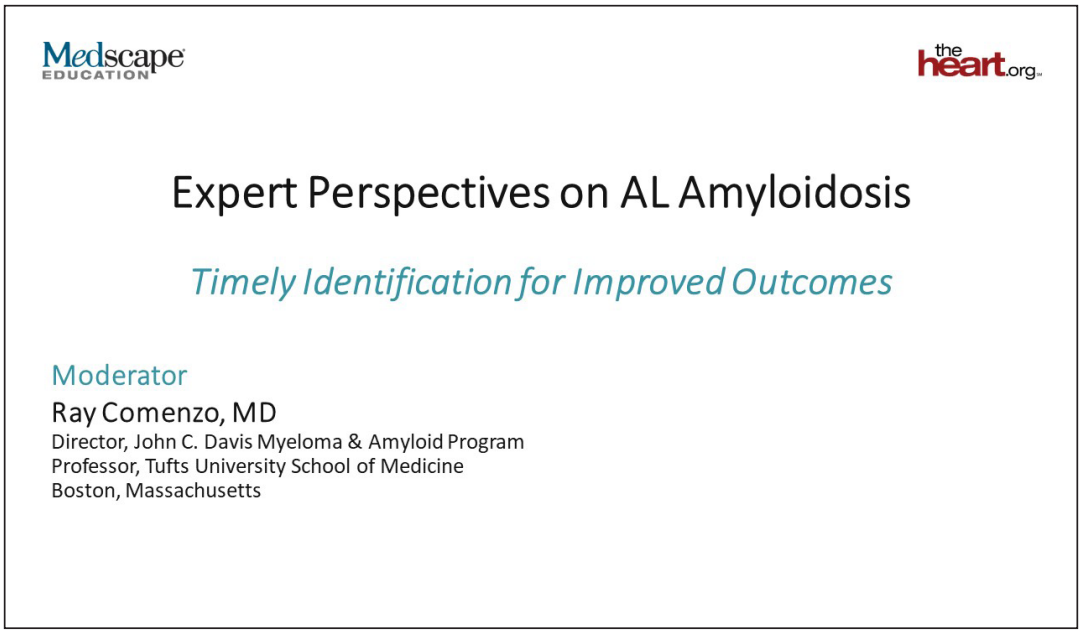
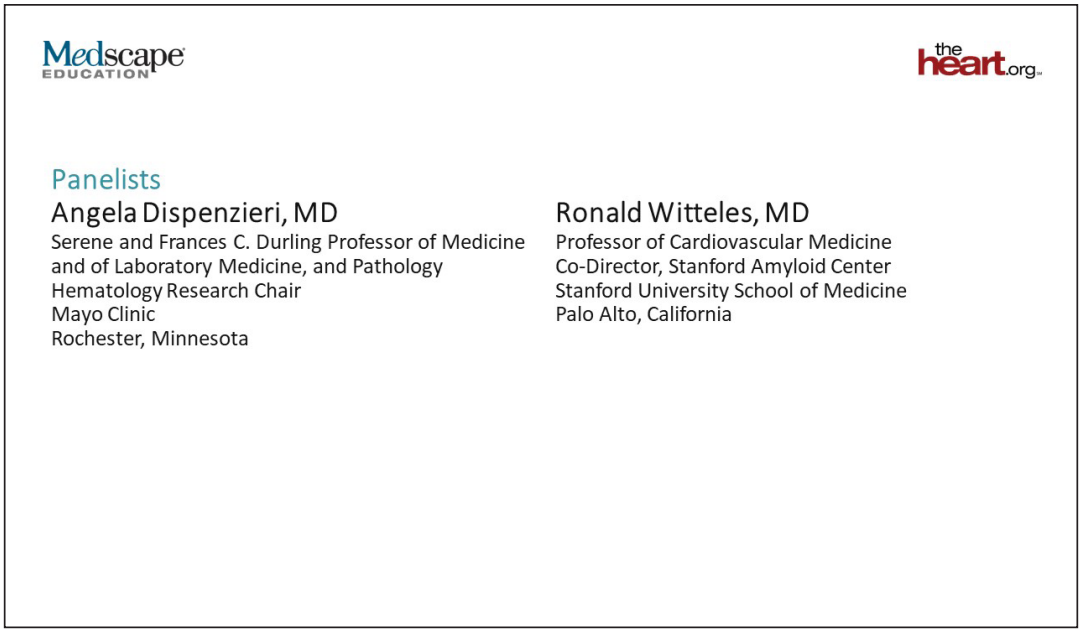
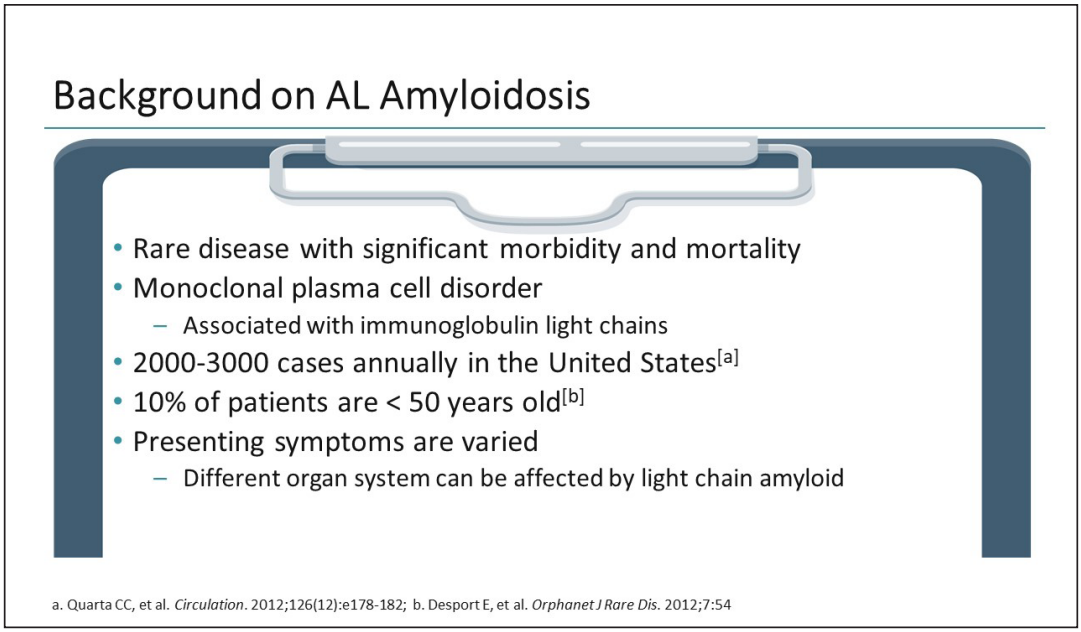


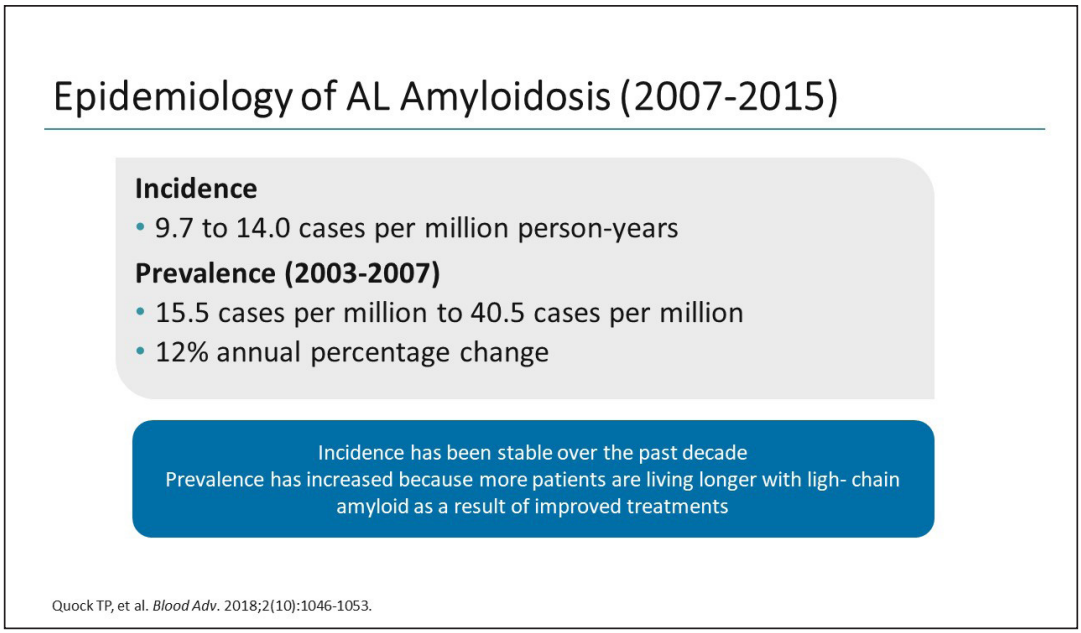
Ray Comenzo, MD: Hello. My name is Ray Comenzo. I'm a hematologist at Tufts Medical Center and I direct the John Davis Myeloma and Amyloid Program.



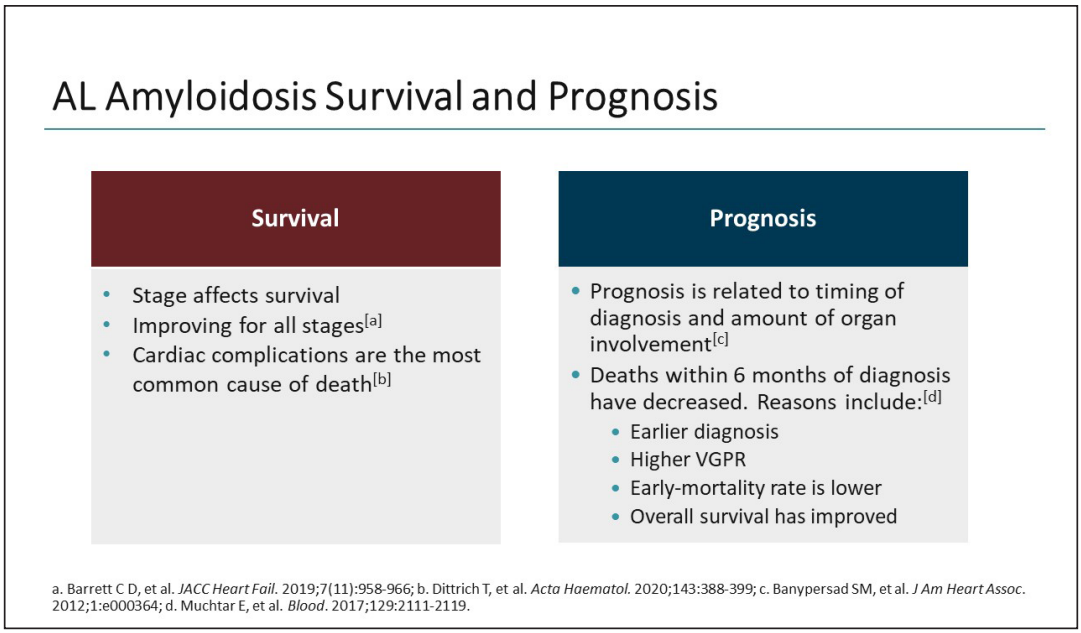
I want to welcome you today to this marvelous program entitled, Expert Perspective on AL Amyloidosis: Timely Identification for Improved Outcomes. I'm joined today by 2 world-class experts, Dr Angela Dispenzieri, who's the Serene and Frances Durling Professor of Medicine in Laboratory Medicine and Pathology and also the Hematology Research Chair at Mayo Clinic Rochester, and Dr Ron Witteles, professor of Cardiovascular Medicine and the co-director of the Stanford Amyloid Center from Stanford University School of Medicine in Palo Alto. Welcome Drs. Dispenzieri and Witteles to this great program.



Dr Comenzo: So let's start by sharing some background details about AL. Obviously, if you're attending this program, you understand that it's a rare disease and is associated with significant morbidity and mortality. It truly is an ordeal for patients. It's a monoclonal plasma cell disorder associated with immunoglobulin light chains. And as you can see from the slide, the majority of patients are over the age of 50; the presenting symptoms are varied because multiple organ systems can be damaged by light chain amyloid.

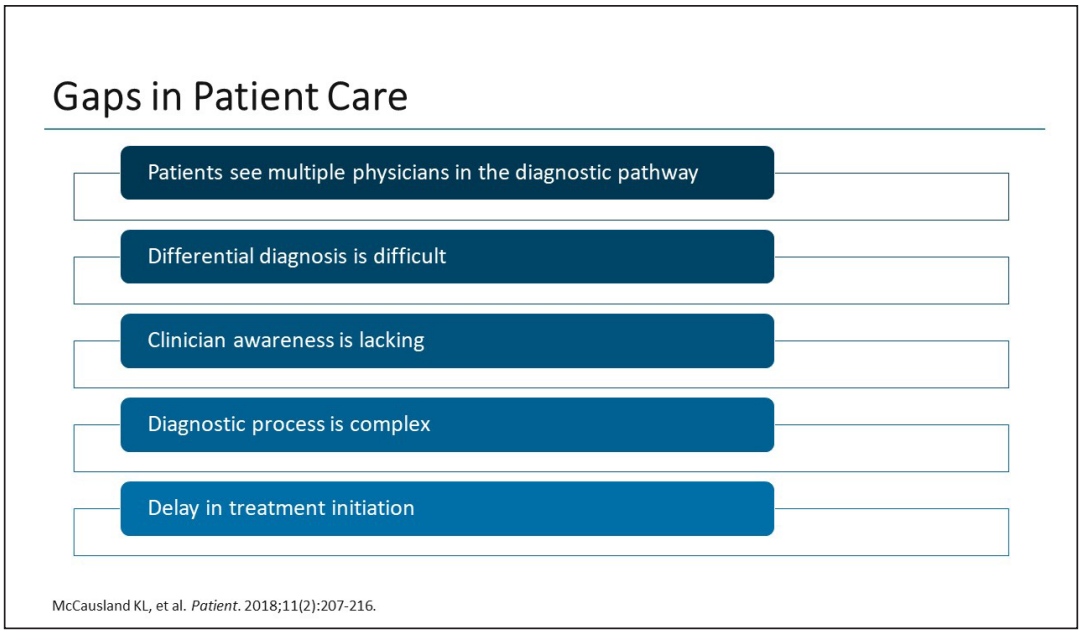


Dr Comenzo: While the incidence has not changed over the past decade, the prevalence has increased because more patients are living longer with light chain amyloid as a result of improved treatments.

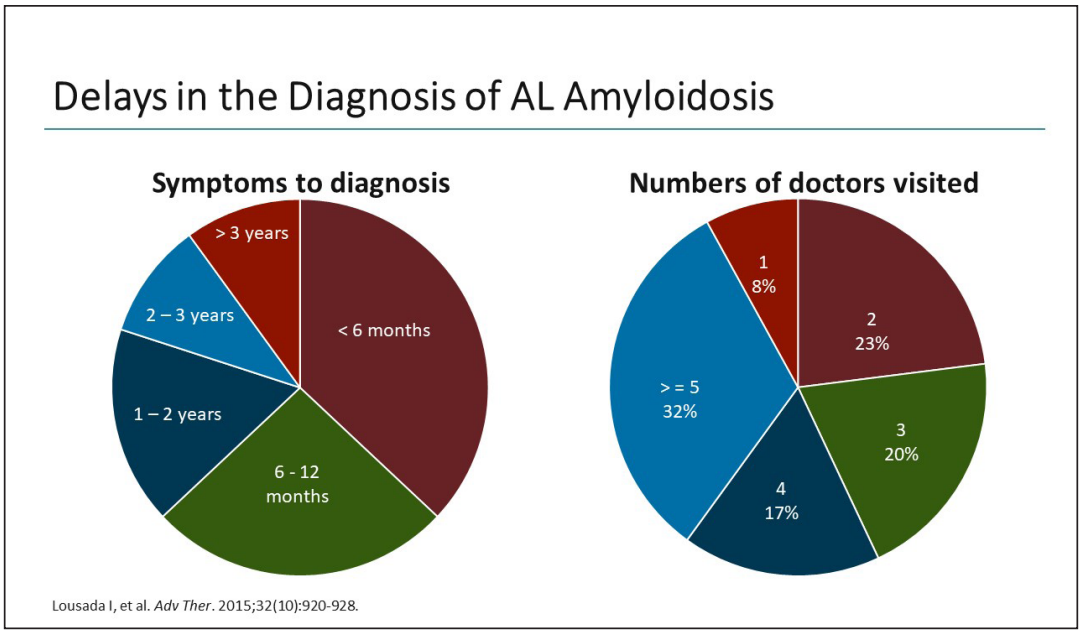


The stages of amyloidosis impact survival. And prognosis, as is stated in the box on the right, is related to the timing of diagnosis. If patients are diagnosed late in the course of disease and have large amounts of organ damage, their survival and certainly their organ function long term are impacted.

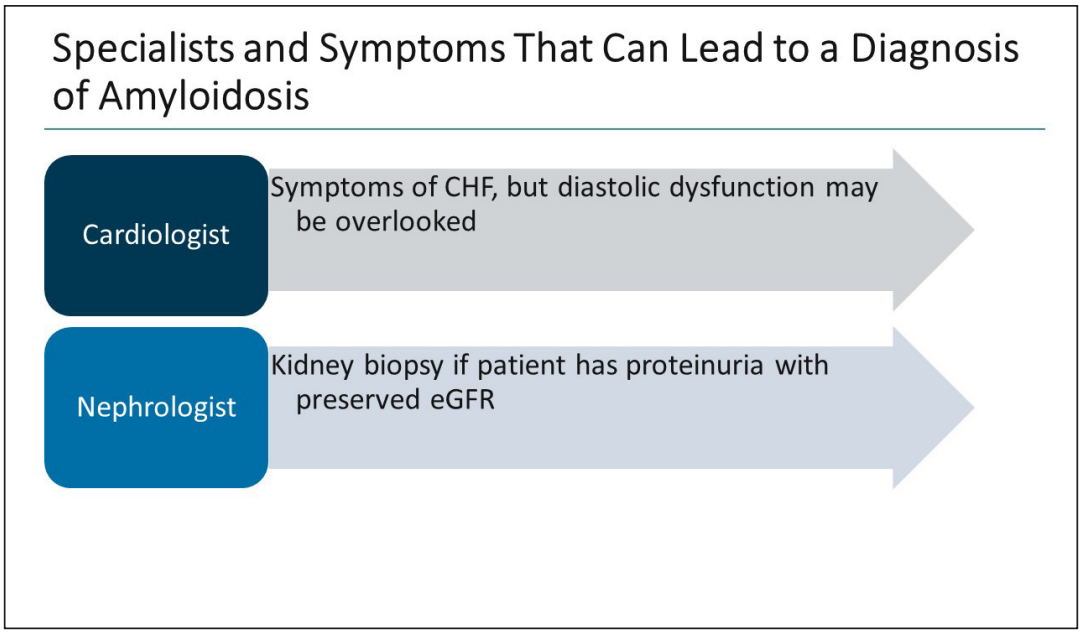
The overall incidence of deaths within 6 months of diagnosis has been decreasing. Early mortality, that is to say, has decreased and overall survival has improved over the course of this century.



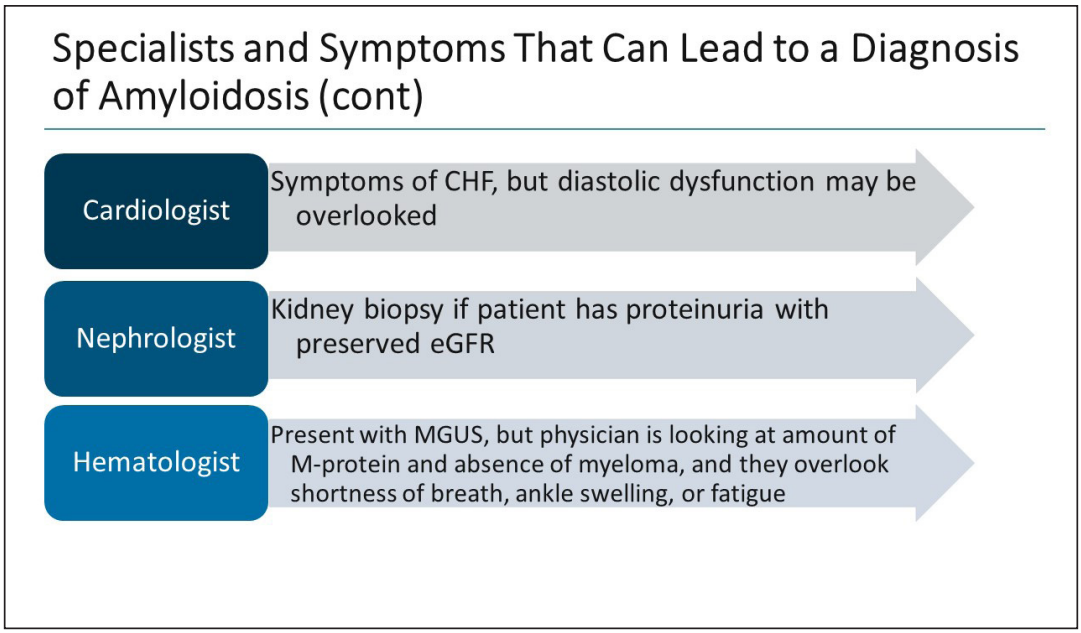
However, patients still experience gaps in care, patients often go to multiple physicians, the diagnosis is tricky to make, as we'll hear from Angela and Ron. And to some degree, the awareness of clinicians remains somewhat problematic. Indeed, adding to these problems is the fact that diagnostic process, as we will hear, is also fairly complex, and therefore there's a prodrome prior to the initiation of active treatment.



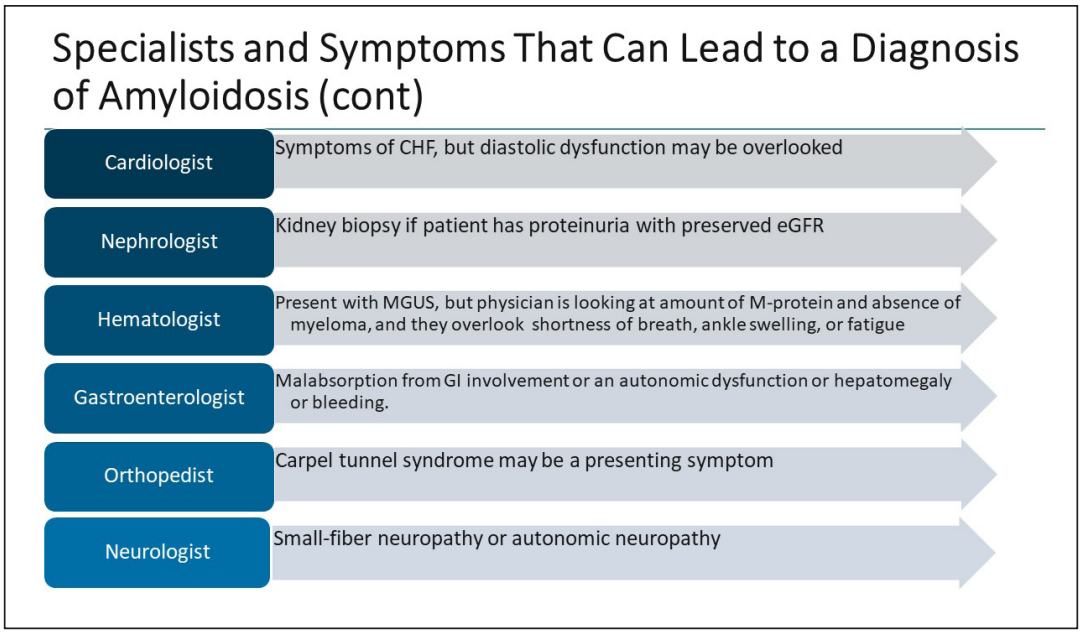
Dr Comenzo: As you can see in this first diagram, this first pie chart, many patients went beyond 6 months until diagnosis, and some went several years. As many patients visited 3, 4, and 5 doctors before the diagnosis was made. So, with that as an intro, let's talk a little more about how we identify, how we diagnose, and how we treat AL amyloidosis. Angela?



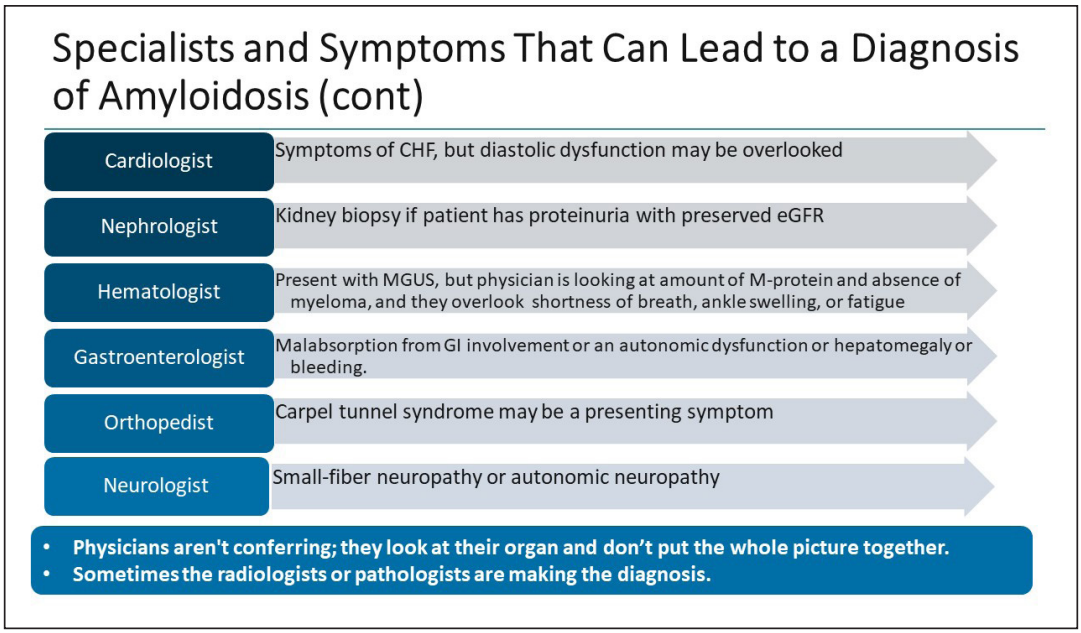
Angela Dispenzieri, MD: Yeah, thanks, Ray. So as you already alluded to, it is a complex disease with sometimes very vague symptoms and it is a challenge for anybody to really come up with a diagnosis. One has to think about it. And so the diagnosis can be made through cardiology, because a patient may come with symptoms of CHF, but if they have diastolic dysfunction that on occasion is overlooked, folks are looking for systolic dysfunction. Patients may present through the door of a nephrologist. They sometimes can do a little better because they're pretty ready with a needle to do a kidney biopsy if something's not quite right. If patients have proteinuria with preserved eGFR, they will often do a kidney biopsy and get the answer.



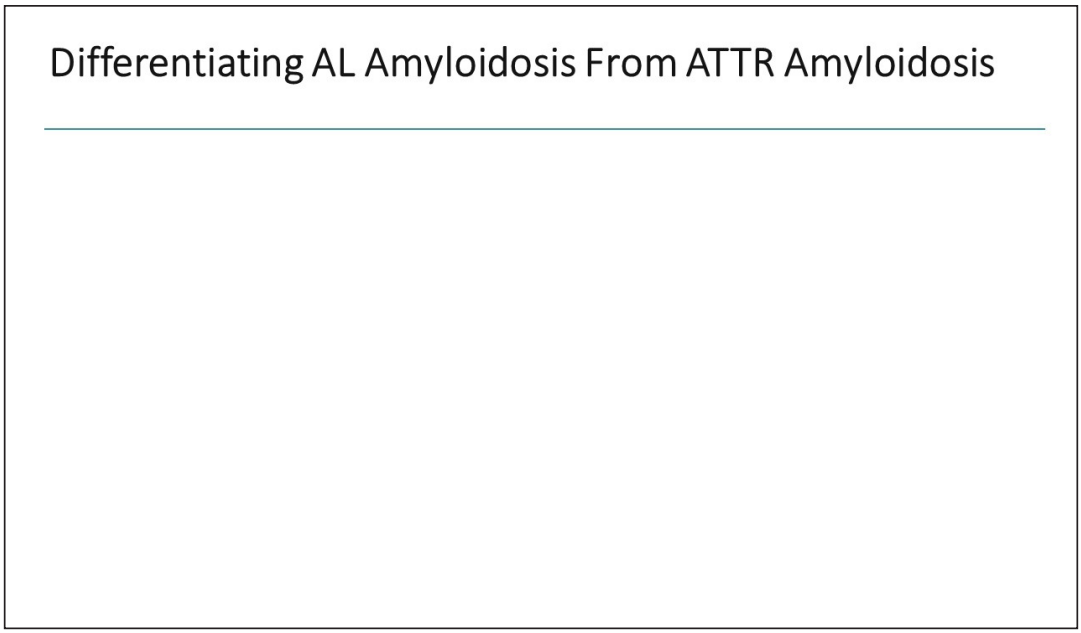
Dr Dispenzieri: Hematologists however, if a patient presents to a hematologist. A patient may look like they have a monoclonal gammopathy of undetermined significance (MGUS) and the physician may just focus on the fact, well your protein's not very big and you don't have myeloma, overlooking the fact that the patient is reporting shortness of breath or ankle swelling or other fatigue. And so again, an MGUS or a smoldering myeloma presentation, it's not just about the size of the monoclonal protein and whether or not a patient has bone lesions.



Patients may present through the door of a gastroenterologist because they have malabsorption from GI involvement or even sort of an autonomic dysfunction that's causing issues for them, or they may have hepatomegaly or bleeding. Even through an orthopedist's door, so carpal tunnel syndrome may be a presenting symptom. Or a neurologist's door because of small fiber neuropathy or autonomic neuropathy.

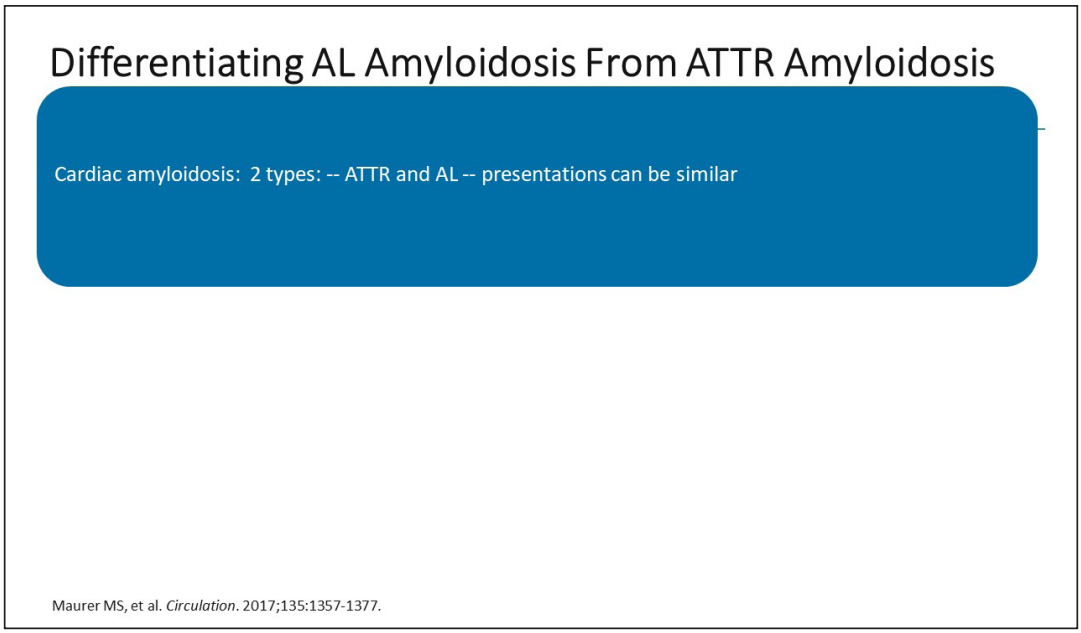


Dr Dispenzieri: And that's really important. Physicians aren't conferring and they're just looking at their organ and not putting the whole picture together and that causes a lot of difficulty for patients. And so sometimes it's not even the clinician who's getting it. It may be, the patient's sent for an MRI of the heart and the radiologist is the one who picks it up. Or it's the echocardiographer seeing the diastolic dysfunction and reduced strain. And sometimes it's a pathologist seeing something incidentally on H&E which isn't that common, but that prompts the Congo red stain. So it is challenging, but I think that people need to keep thinking about it, especially the big specialists,

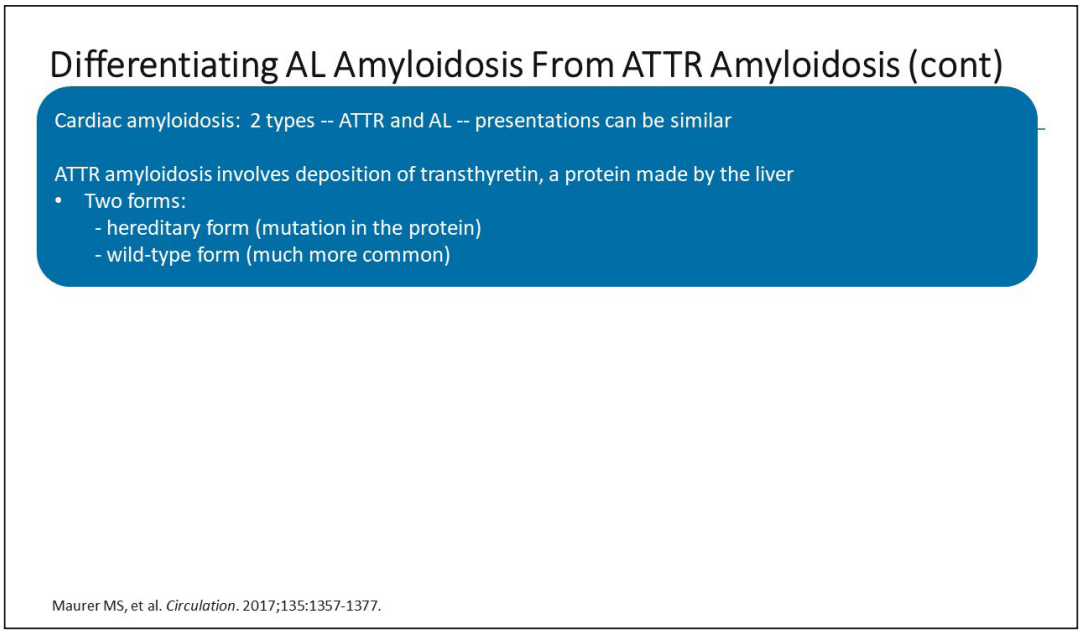


Dr Dispenzieri: Ron, what about the issue of ATTR versus the AL?

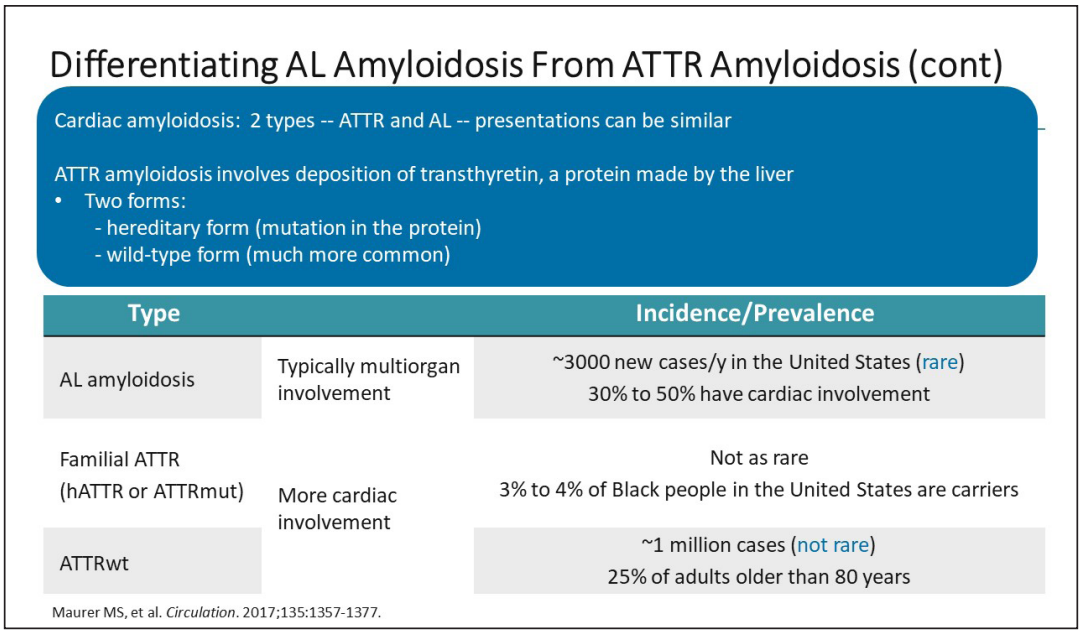
Ron Witteles, MD: Well thanks, Angela. Yeah, those were such great points. I want to emphasize, even before getting into that, to the point that you made because it's so critical for cardiologist. I hated to see on the slide that Ray showed that cardiologists were only in third place for making the diagnosis when heart failure is probably the most common presentation with this disease. And I think a big part of that is this problem that patients will be diagnosed with diastolic heart failure as if that is a diagnosis. And I really want to emphasize, diastolic heart failure is a syndrome, not a diagnosis. And so if you've made that diagnosis, you've only done half your job. And if you don't then ask the question as to why, then you either miss the diagnosis or really miss out on that critical window when you could have started at patient on life-saving therapy.



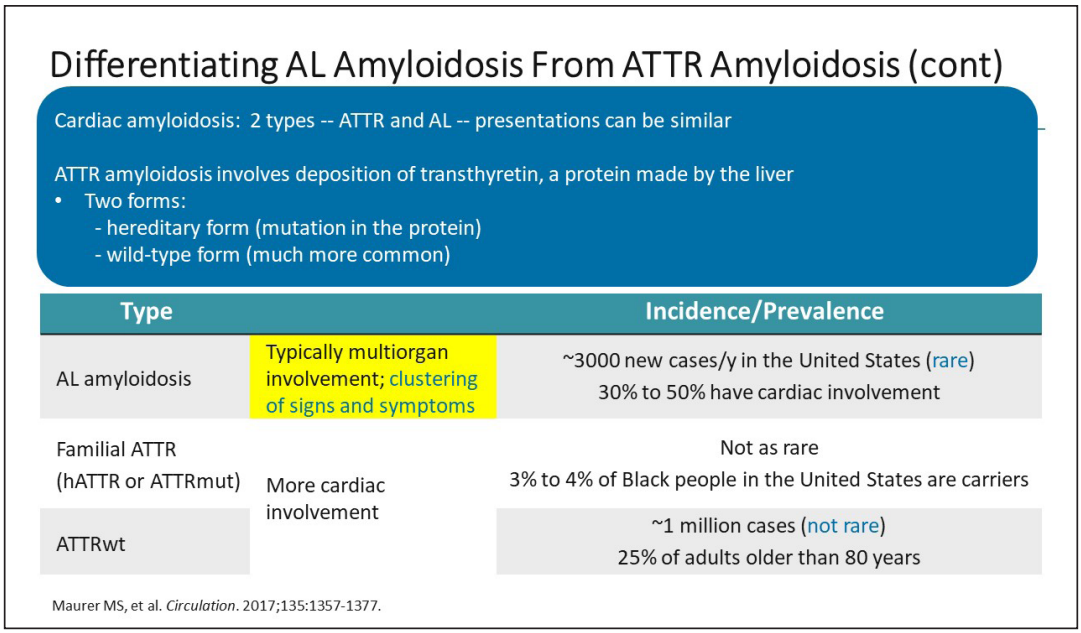
Dr Witteles: In terms of cardiac amyloidosis, it really is 2 main types, AL and ATTR amyloidosis. Though our focus here, of course, today is on AL amyloidosis, it's really important to understand that there is a second type. So that as they will present often quite similarly, and because it's so crucial to make the distinction so that the patient is started on the right therapy.



Dr Witteles: ATTR a myloidosis involves the deposition of transthyretin, a protein that's made by the liver. And there's 2 forms, a hereditary form due to a mutation in the protein, and the much more common wild-type form.

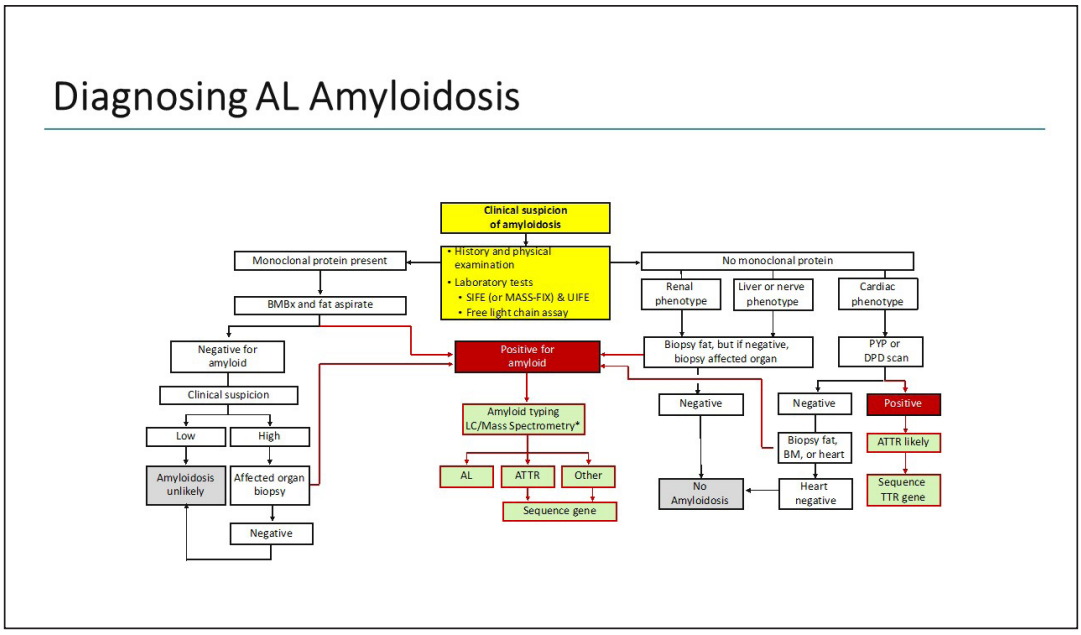


And I think it's really important to think about the epidemiology here, because AL amyloidosis is a legitimately uncommon disease, you might even go as far to say rare disease, not an unheard of disease. Clinicians will see it, but it's fairly rare. ATTR amyloidosis, when you get into the wild-type form, is downright common when you look in the right population, particularly the wild-type form, which is very common in older men. And so it's critical to understand that as a cardiologist, you're going to see ATTR amyloidosis. In fact, you're going to see it frequently. But it's really critical that you not make the assumption when you are diagnosing somebody that it's ATTR, because then you're going to miss the AL patients.

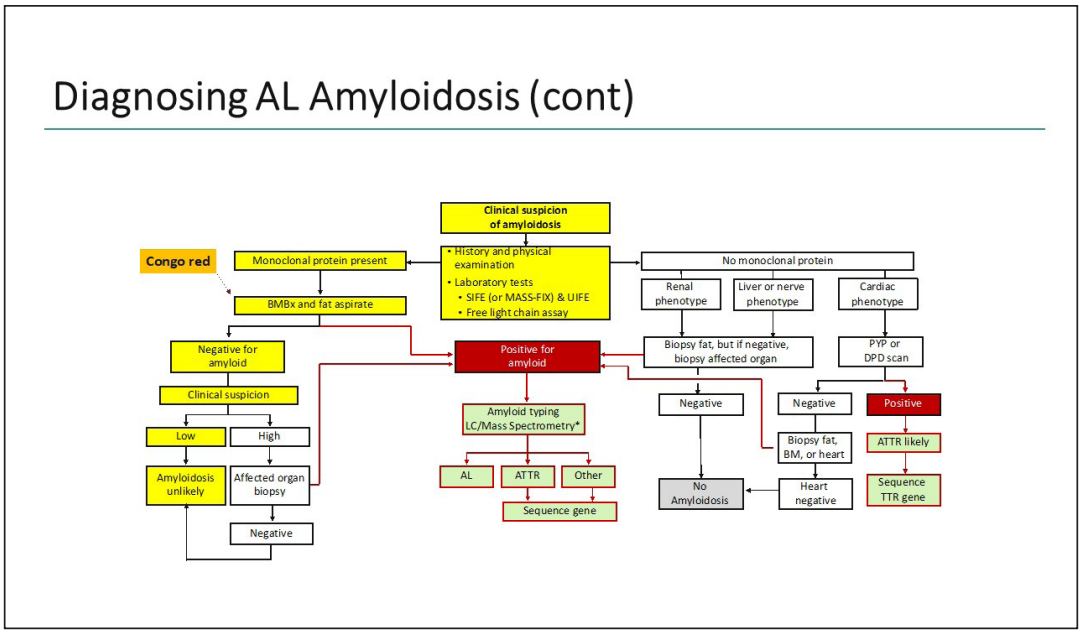


Dr Comenzo: What do we want clinicians to keep in mind when they evaluate someone whose symptoms may be rather vague, who may indeed have heart failure with preserved ejection fraction or a standard monoclonal gammopathy? What do we want those clinicians to think about in terms of next steps in the diagnostic process?

Dr Witteles: Well, I'll say real briefly, and then I'll hand it over to Angela to maybe really go through the diagnostic algorithm, that in terms of being suspicious as a cardiologist for AL, you really want to see this clustering of signs and symptoms of multiorgan involvement, though AL can really only predominantly involve 1 organ, of course it's much more common to involve multiple organs. So somebody's seeing a patient with diastolic heart failure and proteinuria, they should be suspicious. If somebody's seeing someone with diastolic heart failure and new dysphagia, they should be suspicious, so on and so forth. But really with how common ATTR amyloidosis is now, many of us have now recommended that it shouldn't take much more than a diagnosis of diastolic heart failure with a thick heart to be thinking about amyloidosis and ruling it out. And then we get to the diagnostic pathway, which maybe I'll hand over to Angela to tell us about.

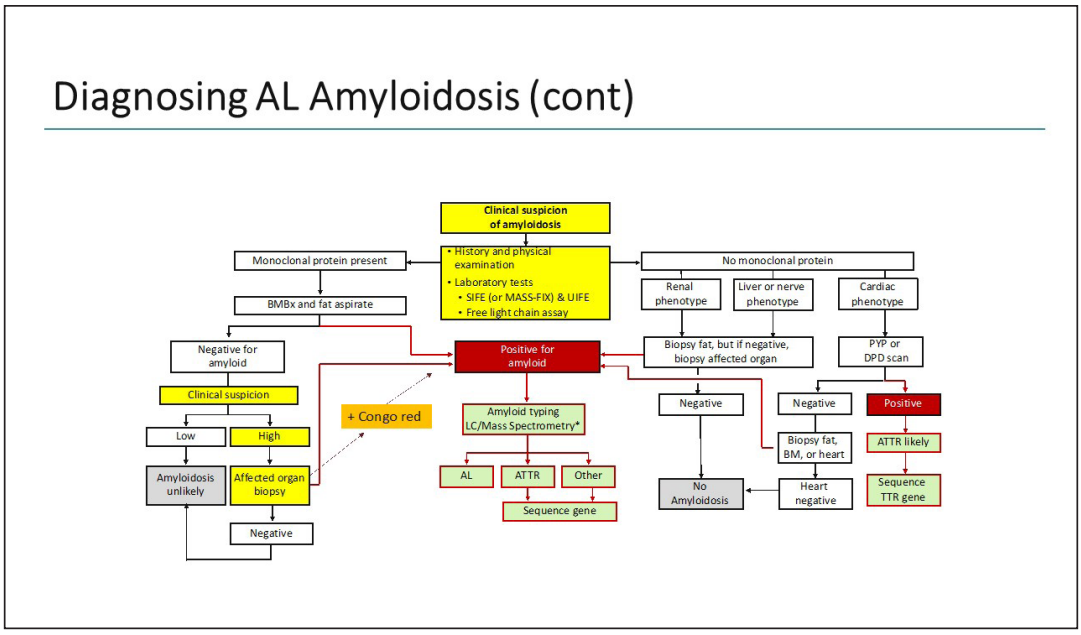


Dr Dispenzieri: Right, so I think it comes down to, the first thing is think of it. And you pointed out to the triggers that should make us think about amyloid and so a good history, physical exam. But the first tests when you're thinking about it are going to be to do an immunofixation of the serum and the urine and the free light chains of the serum.

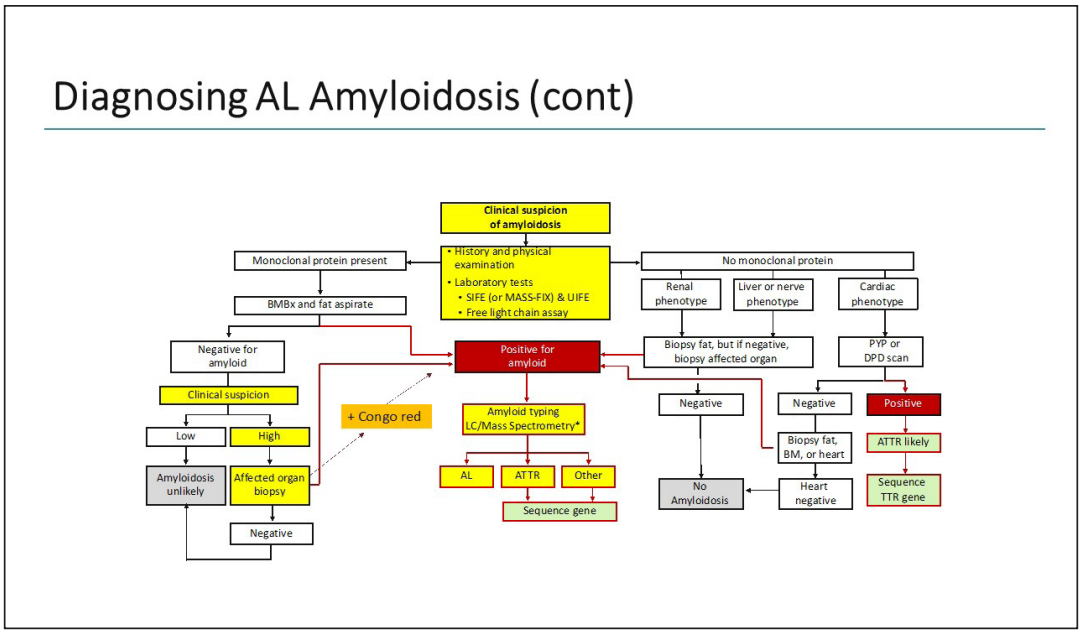


And then you can really break it down into, is there a monoclonal protein present or not? And if there is a monoclonal protein present, then you need to get a tissue diagnosis, and you can do that often just by doing a fat aspirate and a bone marrow biopsy in that patient. You have about 90% sensitivity to pick up AL.

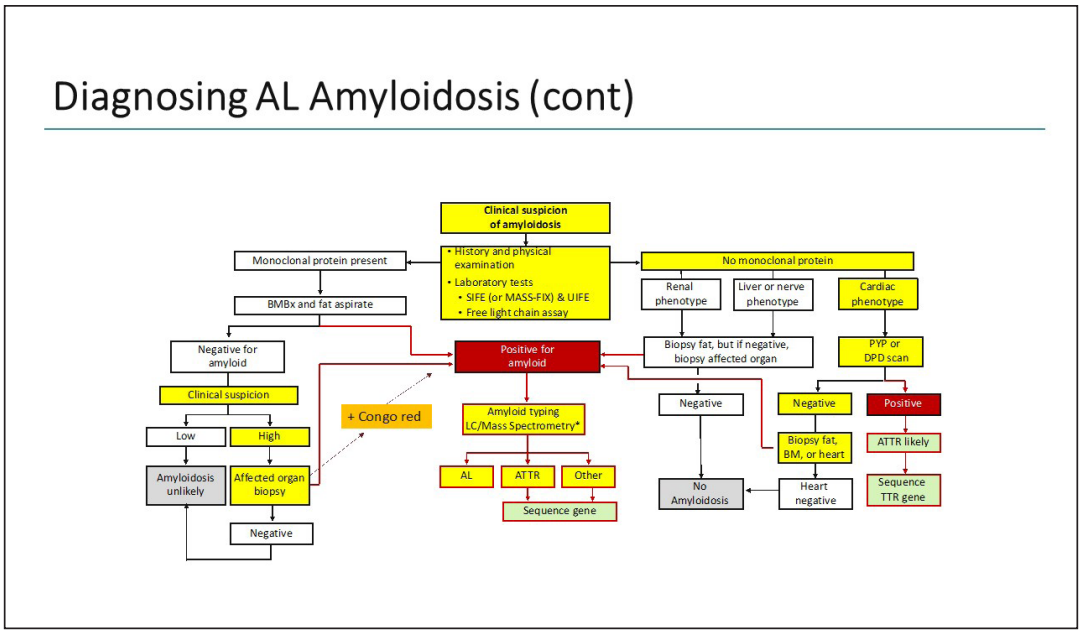
If those tests do not give you AL, so you're doing a Congo red, of course, with those 2 biopsies. If those are negative, you haven't ruled it out 100%. If your index of suspicion is so-so, it's not real high, then you could probably just stop there.



Dr Dispenzieri: But if you really are still not sure and it's bothering you, you think that this could be amyloid involving the heart or the kidney or any other organ, then you have to go to the affected organ. So that will be an endomyocardial biopsy or a kidney biopsy, and so forth. At any point if you get a positive Congo red, it's amyloid; you can't stop there. It's kind of like if your pathologist told you, you did a biopsy and they said your patient has cancer and that was all they're going to tell you, you'd feel like you were left handing quite a bit, right? And you should have that same feeling if they tell you the patient has amyloid, because the next question is, what kind?

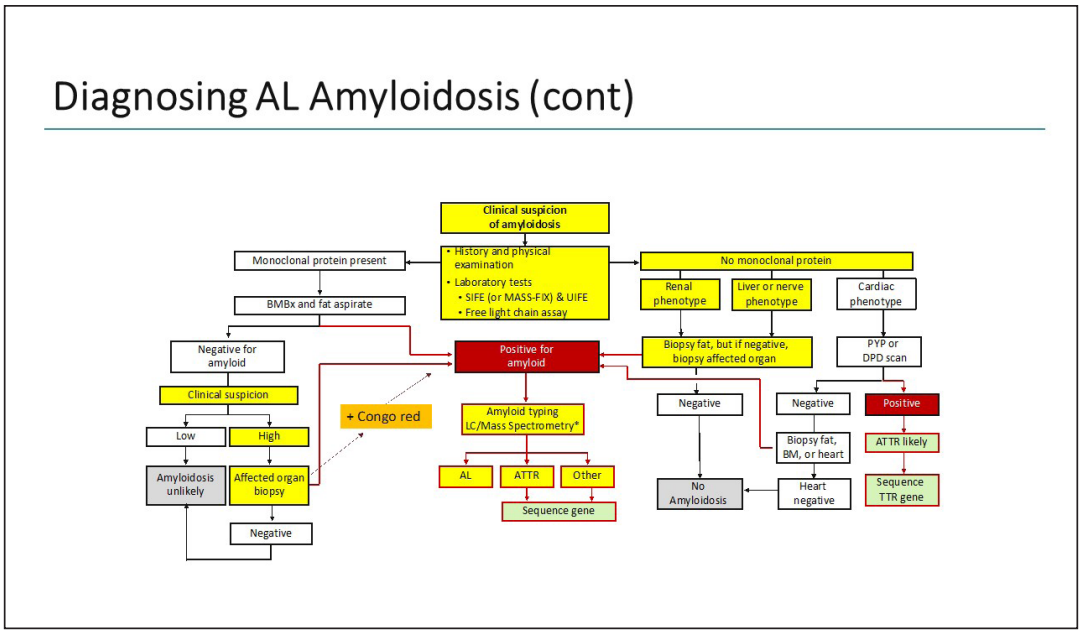


In the US, most of us are doing mass spectrometry of the tissue that tends to be a send out. Immunohistochemistry, it can be done to look at the amyloid, but that's really only in few labs, in Europe mostly, that really do a great job at it. Immunohistochemistry has its problems if it's not a really, really experienced lab. But then, that can tell you, is it AL, is it ATTR, is it another type of amyloid? There are dozens of other systemic amyloidoses. And so that gets you down that pathway.



Dr Dispenzieri: Now, again, remember I said, we started with, is there a monoclonal protein and I said yes. Now it could still be ATTR and an MGUS [monoclonal gammopathy of undetermined significance]. ATTR wild type is a disease of the elderly and, again, they can have MGUS as well and so that's where a tissue biopsy in that instance is going to be really important. But if you did those studies and it was that the monoclonal proteins were negative, so then more often, if it's a cardiac phenotype, then you're going to do, in the US, it's going to be a PYP scan, a Technetium PYP. In Europe often it's a DPD scan. Because those have a pretty good sensitivity and specificity for ATTR amyloid involving the heart.

You cannot just go with a positive 1 of those scans and a monoclonal protein, because we don't know where you are there, because occasionally you can have a weakly positive nuclear scan even in AL, so you really need tissue in that instance.



Dr Dispenzieri: And, again, if it's a renal phenotype or a liver phenotype, then again you're going to need to be going to biopsy that particular organ.

And whenever you come up with amyloid, like I said, only part of the answer, it's not the total answer.

Laboratory Testing in AL Amyloidosis

Test	Ordered to Test for	Normal Range*
SPIE†	Clonal immunoglobulin production	No M spike present
UPIE†	Clonal light chain production	No M spike present
Serum FLC assay	Detecting low-level clonal light chain production; clonality assumed if ratio is far from 1:1	Kappa:lambda ratio = 0.26-1.65‡
Cardiac troponin	Cardiomyocyte injury	Troponin I: <0.055 ng/ml Troponin T: <0.025 ng/ml
BNP or NT-proBNP	Abnormal cardiac function/ heart failure (clinical or subclinical)	NT-proBNP: <300 pg/ml BNP: <100 pg/ml
Urine albumin:creatinine ratio§	Renal injury/proteinuria	<30 mg albumin/g creatinine
Alkaline phosphatase	Hepatic infiltration	35-105 U/l

Adapted from Witteles et al. *J Am Coll Cardiol CardioOnc*. 2019;1:117-130.

And so, what tests: we talked about immunofixation, free light chain. Ray alluded a little bit to the fact that we can stage patients with cardiac biomarkers. So, in all our patients, we're going to do a troponin and a NT-proBNP or a BNP, because we want to be able to prognosticate and those are very valuable for that. You want a 24-hour urine. We can sometimes settle with a urine albumin-creatinine ratio, but I'm old fashioned and I still like the 24-hour urine total protein. And an alkaline phosphatase, also looking at liver as really your bare minimum kinds of testing. And, of course, you do more elaborate testing as indicated.

Imaging of Cardiac Amyloidosis

Increased ventricular thickness on echocardiography

- Due to amyloid infiltration

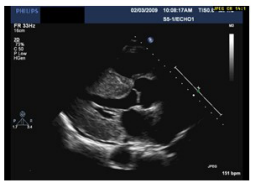


Image adapted from Narotsky DL et al. *Can J Cardiol*. 2016;32(9):1166.e1-1166.e10.

Dr Witteles: When we think about cardiac imaging, it is often what leads people to be suspicious of a diagnosis of amyloidosis, so it's worth having a little sense of what to look for. Classically, we think about increased wall thickness on echocardiography. It will be called left ventricular hypertrophy. It's not, of course, hypertrophy of the myocytes, it's amyloid infiltration, but that's how it looks on echo. What I'd emphasize is, is that you won't always see a massive degree of hypertrophy. Sometimes you will look at it and it kind of comes out and smacks you. But other times it's a lot more subtle and it's really the combination of some increased wall thickness with some other items that should make you suspicious, again things like proteinuria or macroglossia or why is the troponin constantly elevated in that patient, for example.

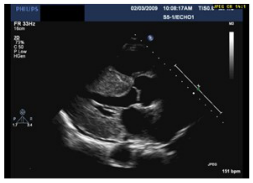
Imaging of Cardiac Amyloidosis (cont)

Increased ventricular thickness on echocardiography

- Due to amyloid infiltration

Abnormal strain imaging

- Apical sparing pattern referred to as "cherry on top"



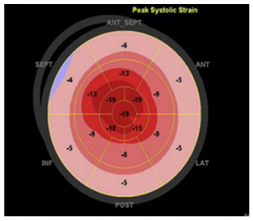


Image adapted from Narotsky DL et al. *Can J Cardiol*, 2016;32(9):1166.e1-1166.e10. Reprinted from Canadian Journal of Cardiology, 32(9), Narotsky, D.L., et al., Wild-Type Transthyretin Cardiac Amyloidosis: Novel Insights From Advanced Imaging, pp. 1166 E1-1166 E10, Copyright 2016, with permission from Elsevier.

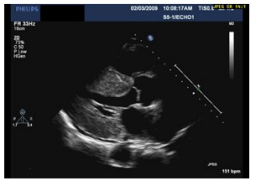
Dr Witteles: There is a very characteristic appearance on strain imaging, sometimes referred to as the cherry-on-top pattern because of a bullseye view of strain as we often show it, it looks red on top, meaning preserved strain at the apex, but gets progressively abnormal as you get more towards the base. One of those things that if you see, should definitely make you suspicious of amyloidosis, but you shouldn't hang your hat on it. The lack of seeing it shouldn't dissuade you from the diagnosis.

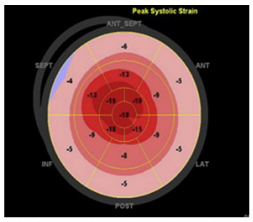
Imaging of Cardiac Amyloidosis (cont)

Increased ventricular thickness on echocardiography
- Due to amyloid infiltration

Abnormal strain imaging
- Apical sparing pattern referred to as "cherry on top"

MRI abnormalities:
- Diffuse DGE
- Difficulty nulling myocardium





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Dr Witteles: There's a very particular pattern on cardiac MRI that if people see, will definitely send them down the route of amyloidosis. From my experience, I think it's less common that somebody orders an MRI specifically querying amyloidosis and more that the cardiologist sees and patient and it's not quite fitting together. The patient has worse heart failure than it looks like the echo should show, they've had persistently positive troponins, very high NT-BNPs, and they say, "Let me get a cardiac MRI to see what's going on." And then the person reading the MRI sees that classic pattern and says, "Hey, think about amyloidosis."

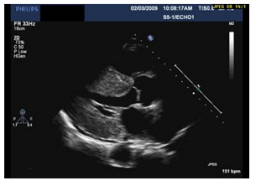
Imaging of Cardiac Amyloidosis (cont)

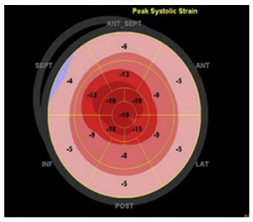
Increased ventricular thickness on echocardiography
- Due to amyloid infiltration

Abnormal strain imaging
- Apical sparing pattern referred to as "cherry on top"

MRI abnormalities:
- Diffuse DGE
- Difficulty nulling myocardium

Combination of increased ventricular wall thickness and low electrical voltages → high specificity … but miss cases!
- More useful: voltage-to-mass ratio





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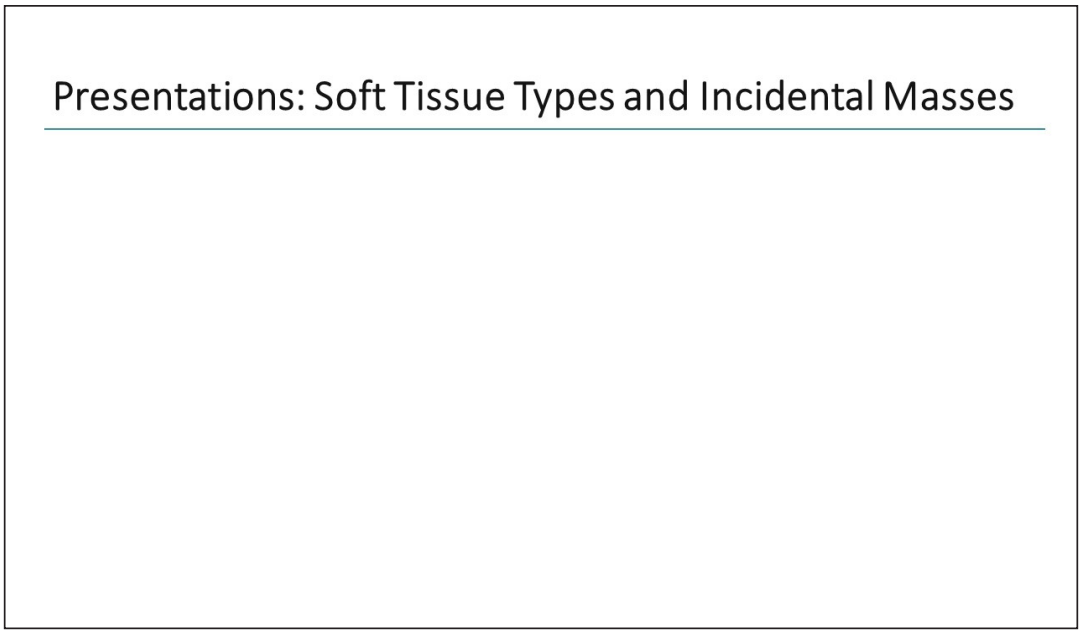
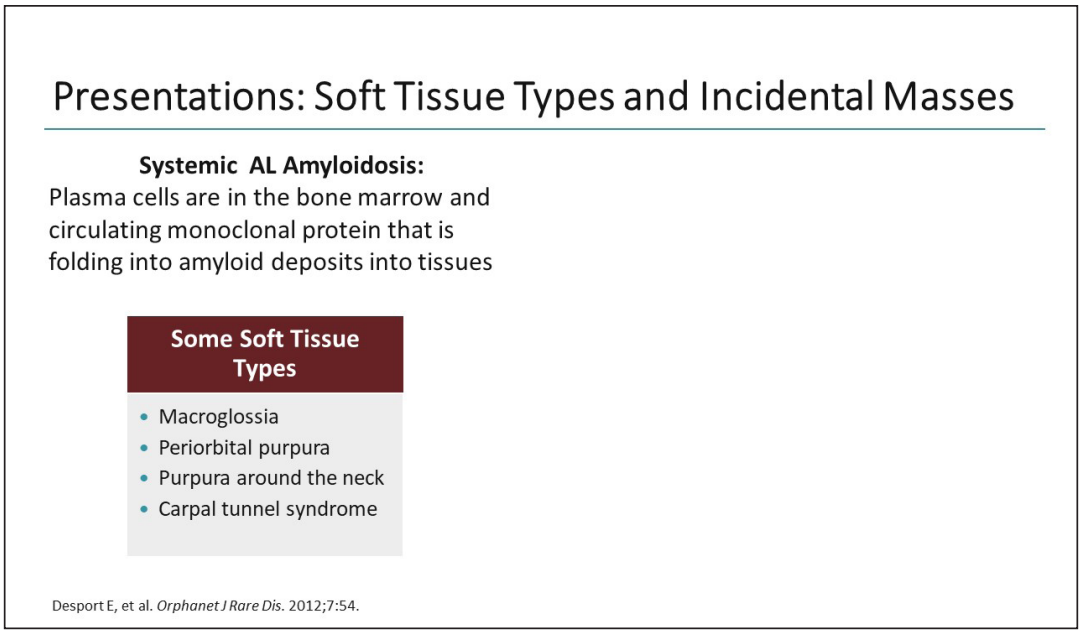
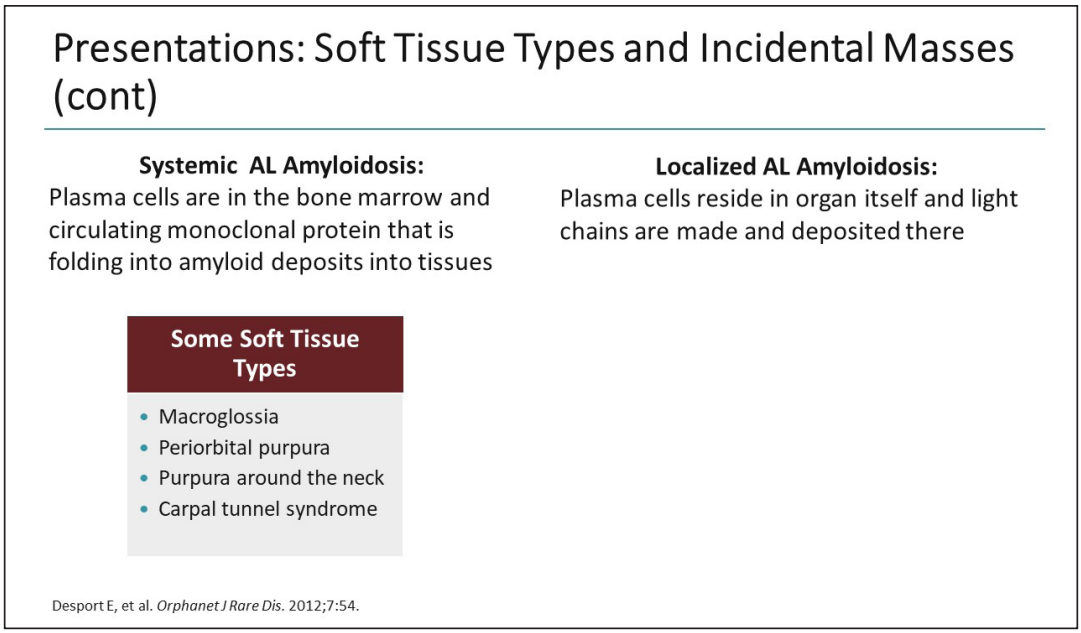
Dr Witteles: And then finally, in medical school, we all learned about that pattern of increased wall thickness on echo and low electrical voltages as sending you down the route of amyloidosis, and it's good to know that. Certainly that's a common pattern. But it's worth noting that often you will not have frankly low electrical voltages, but rather low for the degree of increase wall thickness. And so we often think of it in terms of a voltage-to-mass ratio, so that if the electrical voltages are normal, but there's significant LVH, that should say, wait a second, that's actually low electrical voltages, and you should think about the disease.



Dr Comenzo: I'd like to back up a little bit and get some of your thoughts, both Angela and Ron, regarding some findings on physical exam involving the soft tissues, the ligaments, and perhaps also a comment or 2 about what happens to a patient when a mass, for example, in the lung, is biopsied and there's amyloid there, but the patient is relatively asymptomatic, the mass was picked up because of an incidental CT scan. What are your thoughts, Angela, with those features of exam and of biopsy findings?

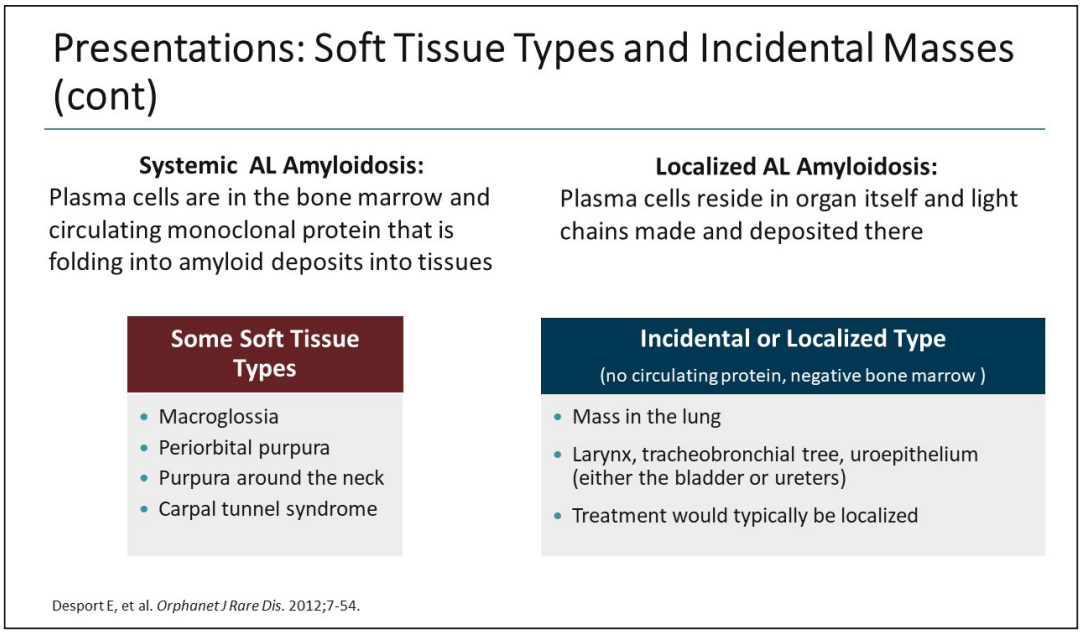


Dr Dispenzieri: Sure, so we learn about macroglossia as a symptom or amyloid, and if you're waiting for that, you're not going to pick up the majority of patients with AL. But certainly you can have macroglossia, you can have periorbital purpura, purpura around the neck, the webbing of the neck and the chest, and the eyes are some of the more common soft tissue things. Certainly carpal tunnel syndrome is a soft tissue finding. And those are some of the major soft tissue types of things that patients will have.



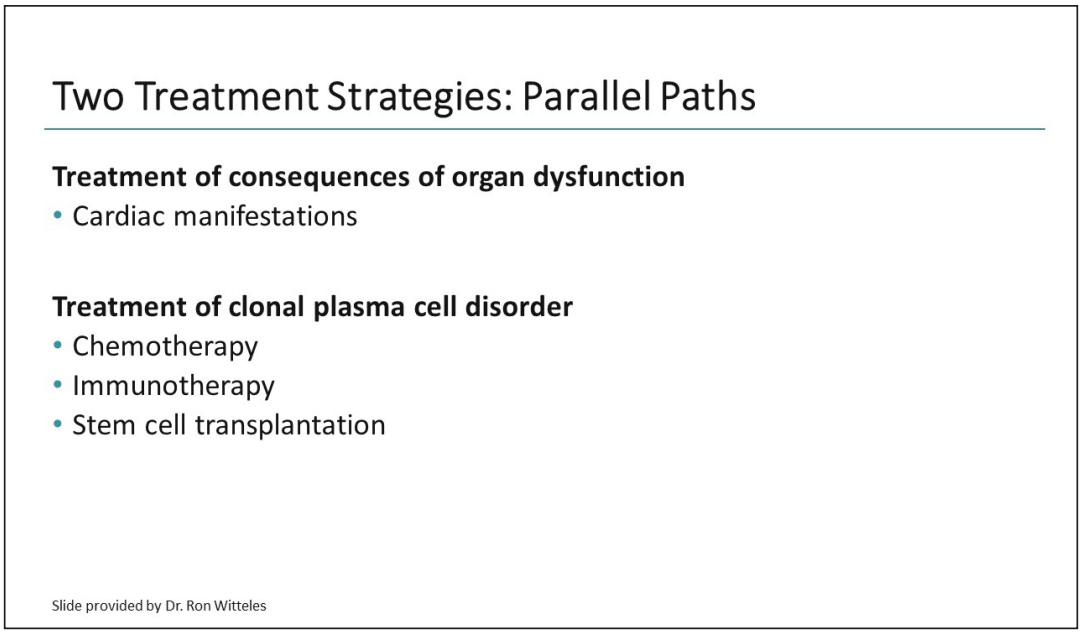
Dr Dispenzieri: In terms of an incidental mass, so that can often get us to what we call a form of localized amyloidosis, so it'll be AL amyloid. So there are few types of localized amyloid as opposed to what we've been talking about as systemic AL amyloidosis. And when we say systemic, we mean that the manufacturing plant of the plasma cells are in the bone marrow and there's a circulating monoclonal protein that then is folding into amyloid and depositing into tissues.

There are types of amyloid where the actual plasma cells are resident in the organ itself and then, just literally, the light chains that they make are just plopping down right there as amyloid and not really circulating around the body.



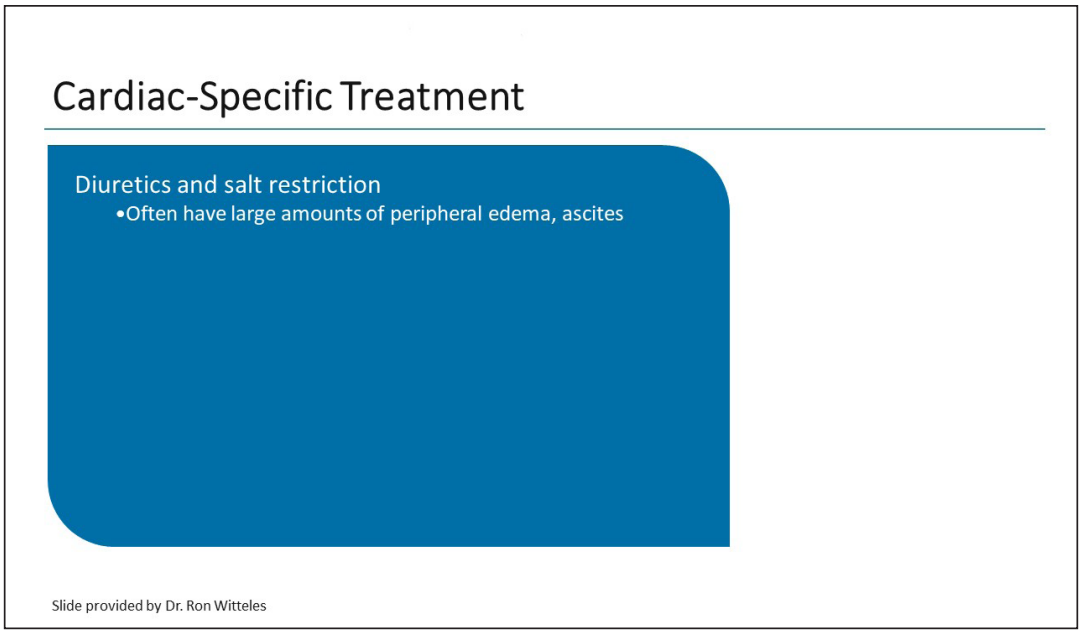
And so that mass that you might find in the lung could be basically a MALToma that has plasmacytic differentiation and an amyloidoma. And those are things that we can actually observe, just like we would observe a low-grade lymphoma.

You can have localized amyloid. Again no circulating protein, negative bone marrow, in the larynx, in the tracheobronchial tree, in the uroepithelium, so either the bladder or even the ureters, are some of the classic, localized AL types of presentation that would not typically warrant chemotherapy. It's more of a localized approach.

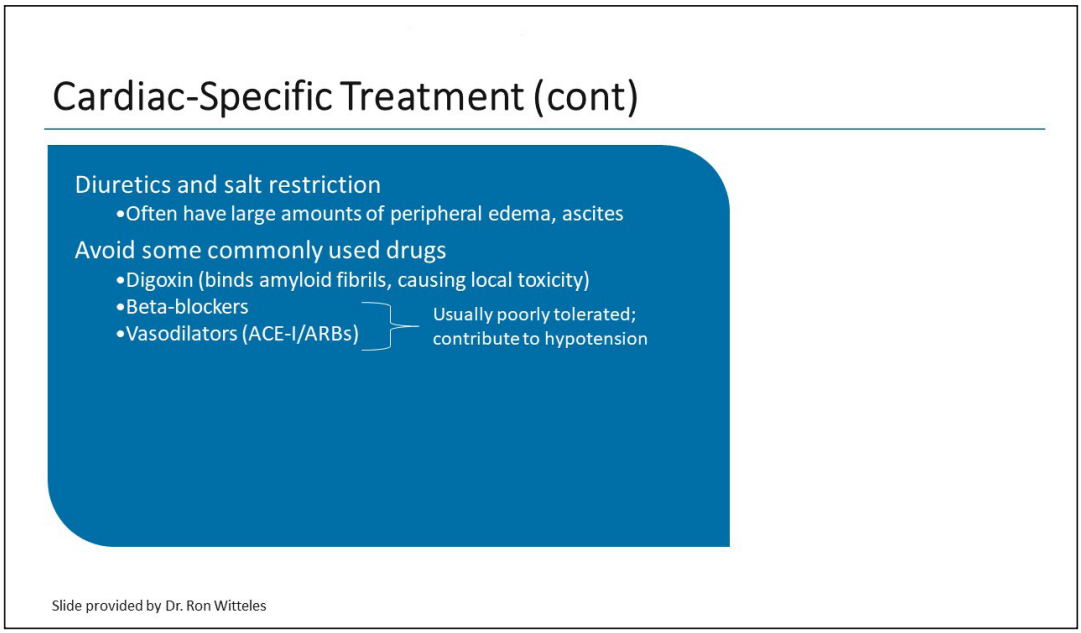


Dr Comenzo: We have highlighted some of the challenges in thinking about amyloid and diagnosing it. Let's talk about the treatments, Ron. What do we have currently and what's on the horizon?

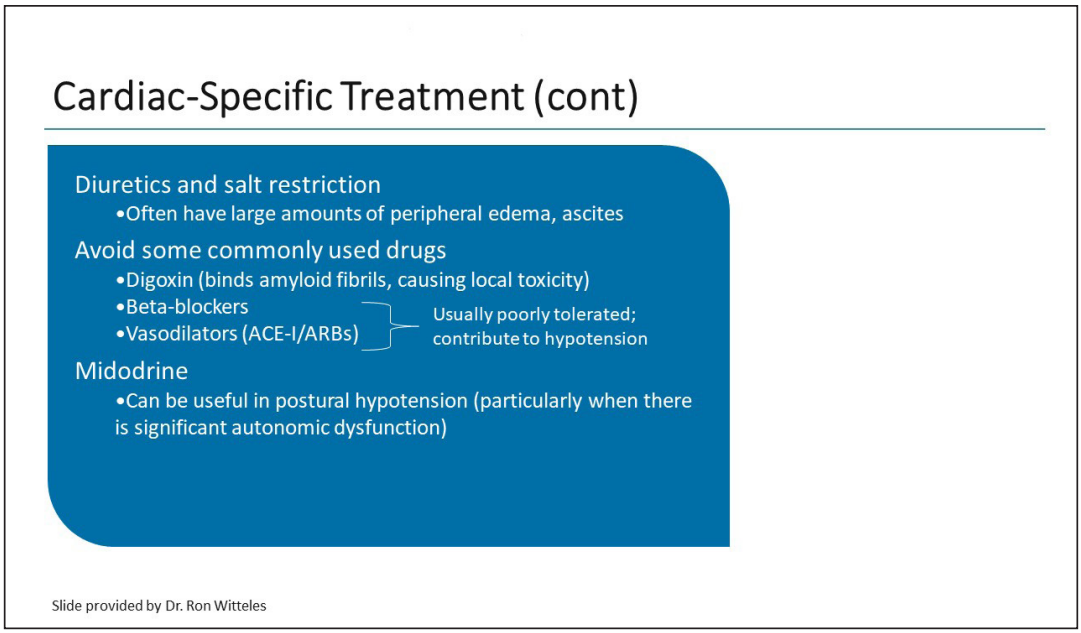
Dr Witteles: Thanks. I always like to describe it to patients that we have to go down parallel paths for treating AL amyloidosis involving the heart. And 1 path, which I'm going to defer to you and Angela on as the real experts, is the treatment of the underlying clonal plasma cell disorder, whether it be with chemotherapy, immunotherapy, or stem cell transplantation. The other part of equal importance is to treat the consequences of the organ dysfunction and, of course, and I say this not only as a cardiologist, the most important 1 to treat [is] the cardiac manifestations, because it is the number 1 cause of death by far in these patients.



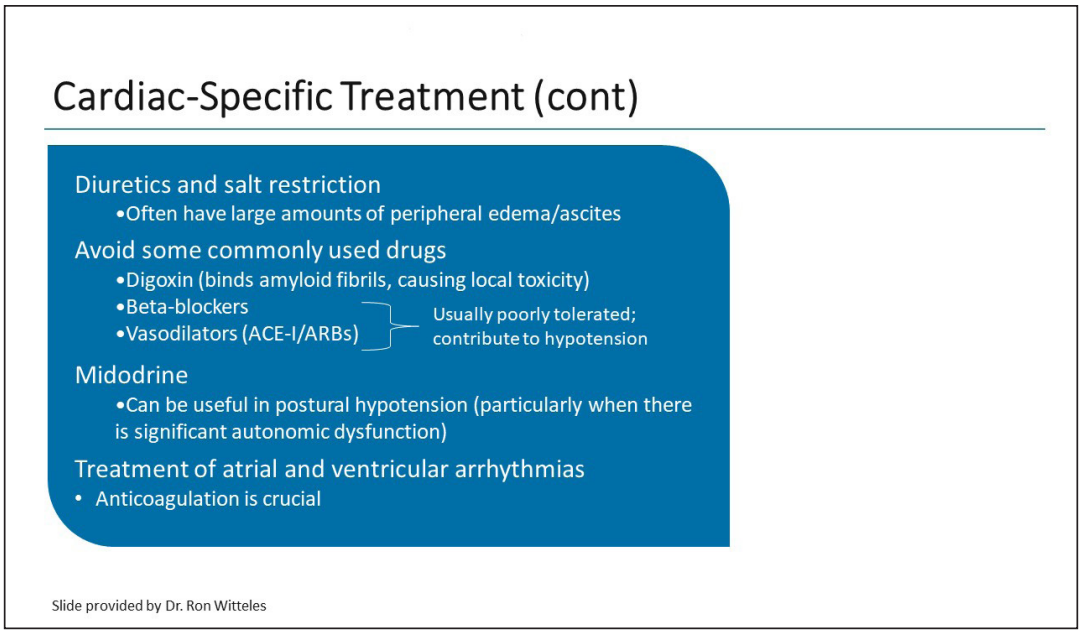
Dr Witteles: And there's a few important considerations. So number 1 is to make sure that patients are being appropriately diuresed. You have to push forward with the diuretics to get volume control. Salt restriction is particularly critical in this population as it is in diastolic heart failure in general.



Dr Witteles: You want to avoid some of the common drugs that we use for other forms of heart failure. Digoxin carries a relative contraindication as it can bind to amyloid fibrils and cause local toxicity with normal serum levels. And then beta-blockers and vasodilators are usually very poorly tolerated because of the small cavity, the small stroke volume that you get contributing to hypotension, and often the autonomic dysfunction contributing to hypotension. And then with beta-blockers, the risk of heart block and sinus node dysfunction. If you have to control atrial fibrillation, yes, sometimes we will use a beta-blocker if no other choice, and sometimes amiodarone will be used as well.

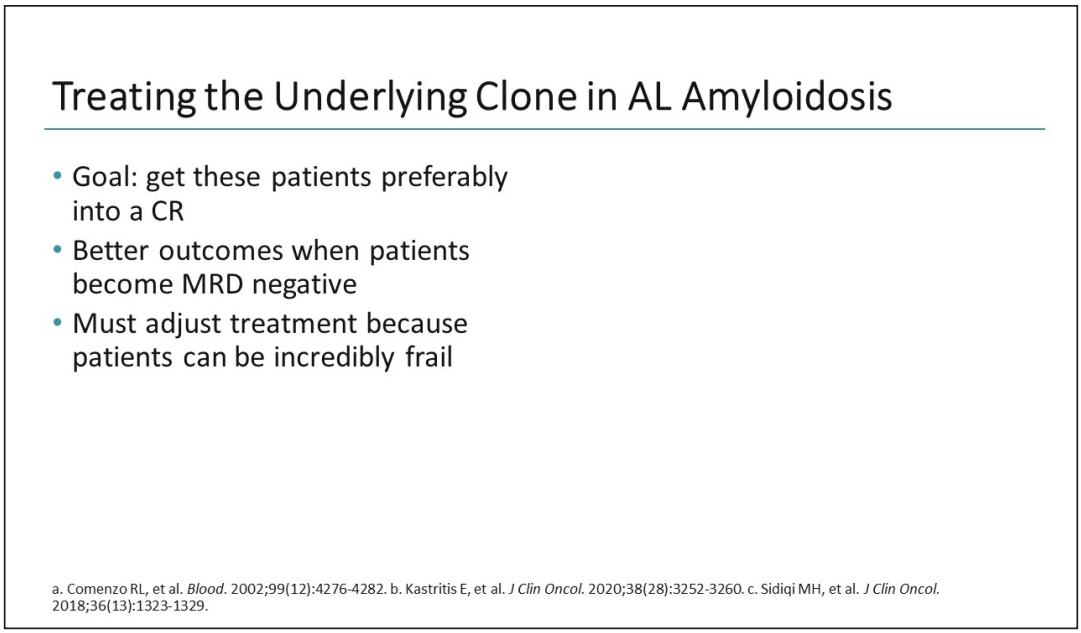


Dr Witteles: Midodrine, in fact, a drug that we rarely use otherwise in heart failure management, can be quite helpful in this disease, particularly when there is quite significant autonomic dysfunction and that's the only way to keep the blood pressure up as you're getting the volume off. In patients with really bad nephrotic syndrome, sometimes you have to do intermittent albumin infusions to get them through it until, hopefully, you get control of the real severe albuminuria.



Dr Witteles: And then finally, the other important part from a cardiac stand point is rhythm management. Atrial arrhythmias are very common. If you can maintain sinus rhythm, that's often helpful in these patients, although sometimes inevitably you can't. Anticoagulation is crucial, and clots are so common in this disease, particularly because of the low flow that patients will have, that, in general, transesophageal echocardiograms are recommended before cardioversion in every single case, even if the patients have been on appropriate systemic anticoagulation.

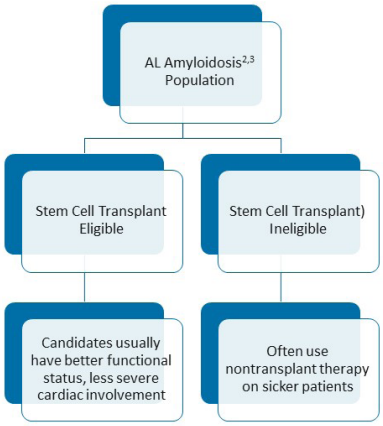
Dr Witteles: And then finally, ventricular arrhythmias are quite common. It is debatable in terms of the use of ICDs for primary prevention in this disease, although our general practice is that as prognosis has gotten so much better, that for patients who have significant cardiac involvement, a reasonable prognosis, and either a suspicious history or a significant burden of non-sustained VT seen on ambulatory telemetry, we will often refer patients for ICDs. Though again, there's reasonable variation in practice on that point.



Dr Dispenzieri: Ideally, we would love to have a way of vacuuming amyloid out of the tissues, but at this point we're still working our way through the possibilities of antibodies that can help us do that. So really the mainstay of therapy, besides the supportive care, is to treat the underlying clone, and so we borrow from multiple myeloma and we're using a lot of those therapies. And our goal is to get these patients, preferably into a complete response; we know that we get better outcomes when patients do get to MRD negative, but we have to balance that frailty issue with these patients because they can be incredibly frail.

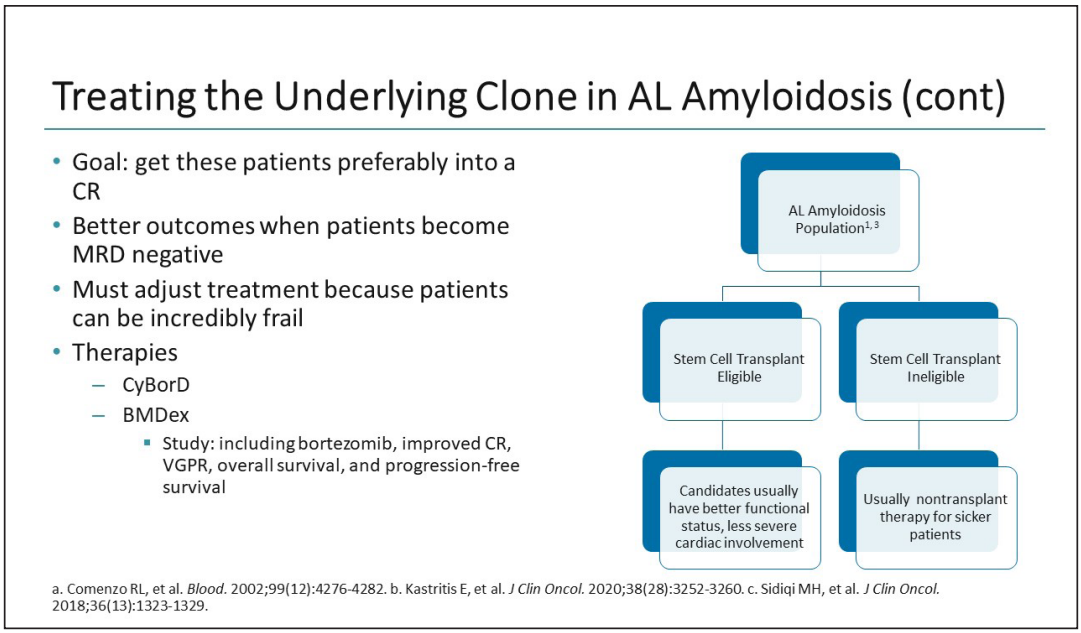
Treating the Underlying Clone in AL Amyloidosis (cont)

- Goal: get these patients preferably into a CR
- Better outcomes when patients become MRD negative
- Must adjust treatment because patients can be incredibly frail



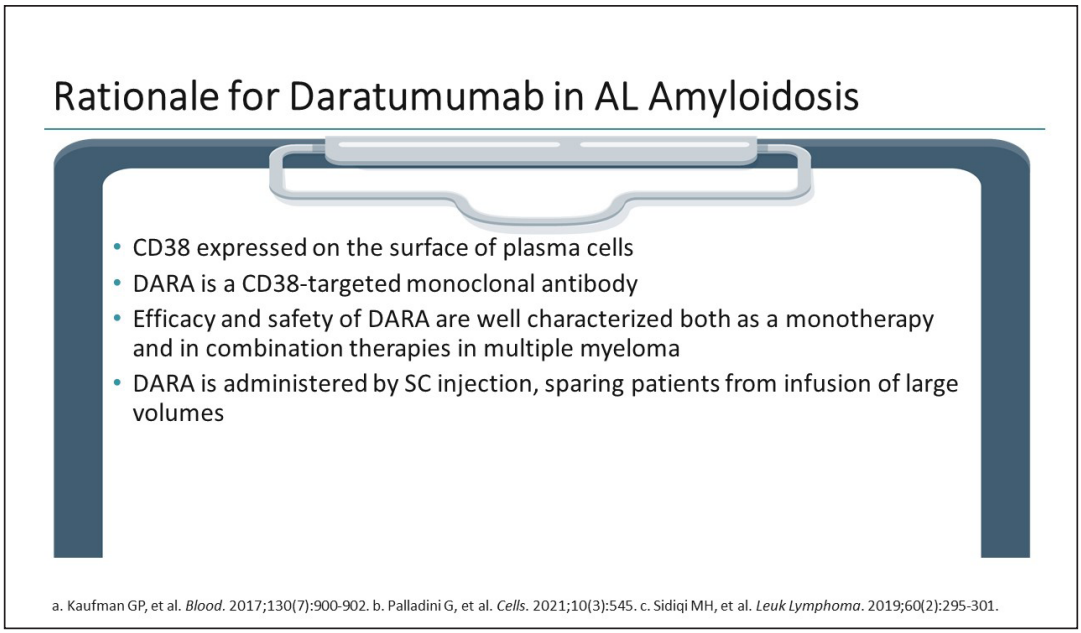
a. Comenzo RL, et al. *Blood.* 2002;99(12):4276-4282. b. Kastritis E, et al. *J Clin Oncol.* 2020;38(28):3252-3260. c. Sidiqi MH, et al. *J Clin Oncol.* 2018;36(13):1323-1329.

When we think about how to treat the underlying clone, we will often, at least in the US, I think, break the patients up into whether the patient's a transplant candidate or not, stem cell transplant candidate. And, in general, stem cell transplant candidates are those patients who have overall better functional status, less severe cardiac involvement, and then we'll often use nontransplant therapy for the sicker patients.

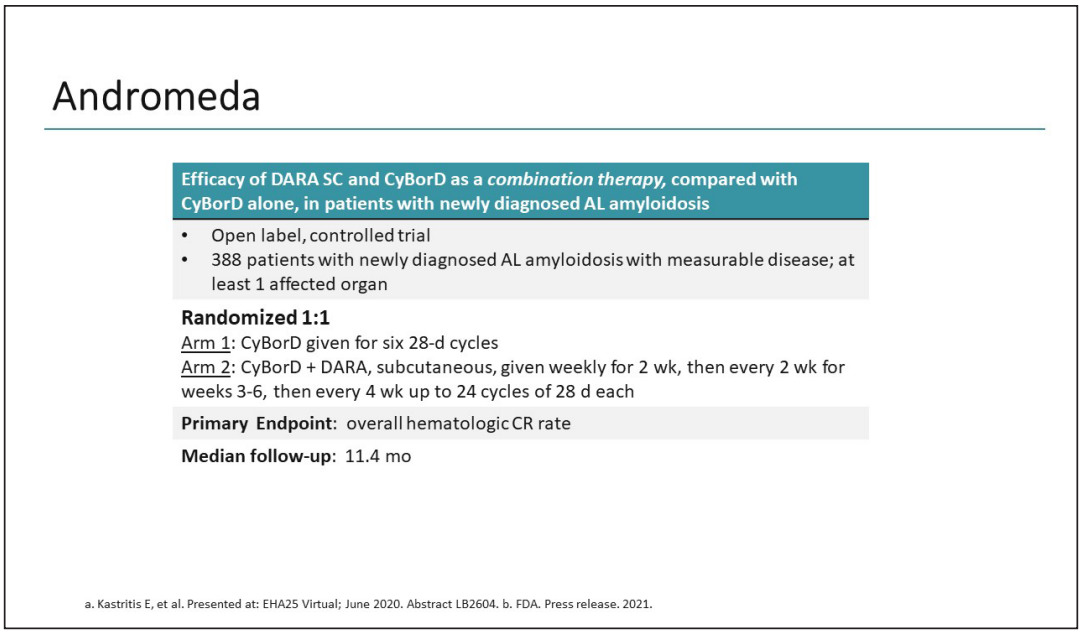


Dr Dispenzieri: But, that said, the important things to think about in terms of some of our favorite therapies, up until just recently, and I'll leave that exciting data to Ray, but where we are up front is commonly in the nontransplant we're going with CyBorD. There was a really wonderful study that was just published the end of last year doing melphalan and dex vs bortezomib, melphalan, and dex; and it was very clear that adding the proteosome inhibitor made a huge difference in terms of the overall very good partial response, complete response. So 64% vs 39% with an improvement in overall survival and progression free survival. And so that is something important and quite notable.

Dr Dispenzieri: Again, the outcomes that we would expect with high-dose melphalan, we have some of the very best outcomes in these patients with a high percent are going to be alive at 10 years or so. We do have to remember that these were some of the better patients at the get go. But we do know that duration of response can be quite long with stem cell transplant. And we do know that in places where there's experience; and over the past 30 years, the treatment-related mortality has decreased substantially using high-dose melphalan with stem cell transplant, in part because we're bringing slightly healthier patients, and also, I think patients are going to centers with a greater experience in terms of transplanting these patients, because there is a little bit of an art to that as well.



Dr Comenzo: The rationale for using the monoclonal antibody daratumumab in patients with AL amyloidosis was based on the fact that the protein on the surface of plasma cells, CD38, which is an ectoenzyme, is the target for daratumumab. Daratumumab had been shown to be quite active in multiple myeloma, a cousin plasma cell disease, What was most interesting about the preparation of daratumumab used in the phase 3 trial, that was called ANDROMEDA, is that daratumumab was given subcutaneously, a brief injection under the skin of the stomach, sparing amyloid patients of infusions of a half a liter or a liter. The infusion of a liter of drug can get someone with cardiac amyloid into trouble.



Dr Comenzo: So daratumumab was added to a standard regimen that Angela just described, a combination of cyclophosphamide, bortezomib, and dexamethasone in 1 group of patients on ANDROMEDA and the other group of patients was treated with standard therapy: cyclophosphamide, bortezomib, and dexamethasone; it's either called BCD or CyBorD. Not only was it safe, but it was extremely active.

Dr Comenzo: The primary endpoint was the hematologic complete response rate and the secondary endpoint was a composite endpoint of major organ deterioration progression free survival, and the overall survival, obviously, was an important secondary endpoint as well as safety.

ANDROMEDA: Results
Response to Dara-CyBorD in AL Amyloidosis

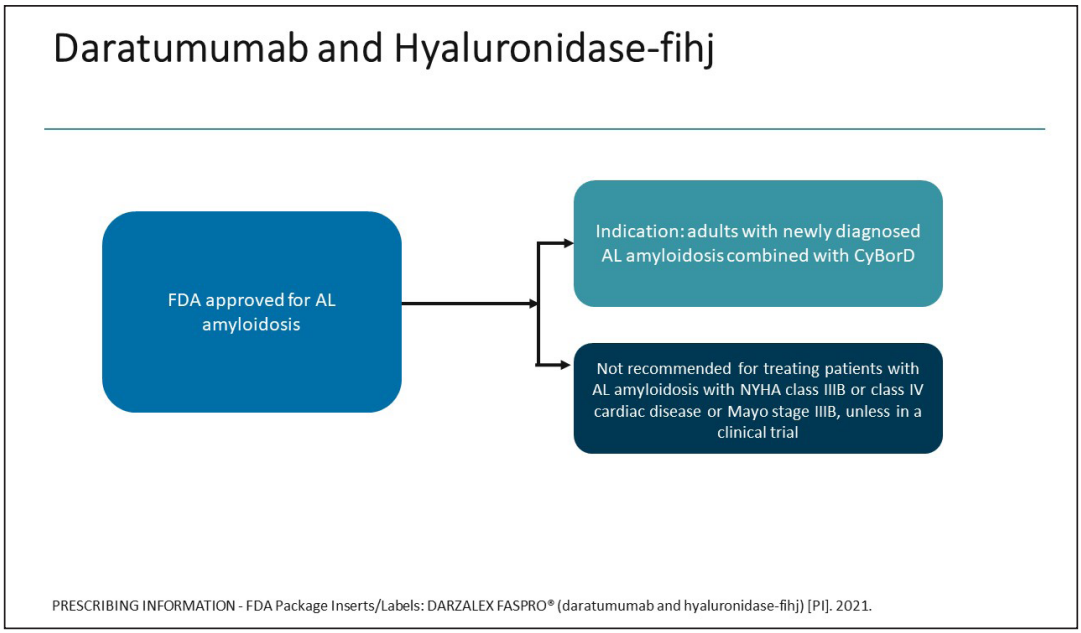
Efficacy	DARA-CyBorD	CyBorD	*P* value
CR at 6 mo	53%	18%	< .0001
Overall hematologic response	92%	77%	
➢ VGPR	79%	49%	
6-mo cardiac response rate	42%	22%	.0029
MOD-PFS	HR, 0.58		.0224

Results: DARA-CyBorD compared with CyBorD alone: better hematologic responses and clinical outcomes.[a]

a. Kastritis E, et al. Presented at: EHA25 Virtual; June 2020. Abstract LB2604. b. FDA. Press release. 2021.

Dr Comenzo: It was a large, global trial and what we learned was that daratumumab marginally increased the rate of complete responses. At 6 months, the response rate in the Dara-CyBorD arm was 50% or more and it was much lower in the CyBorD arm. In addition, the overall response rate was much higher; 80% of patients had a very good partial response or better in the Dara-CyBorD.

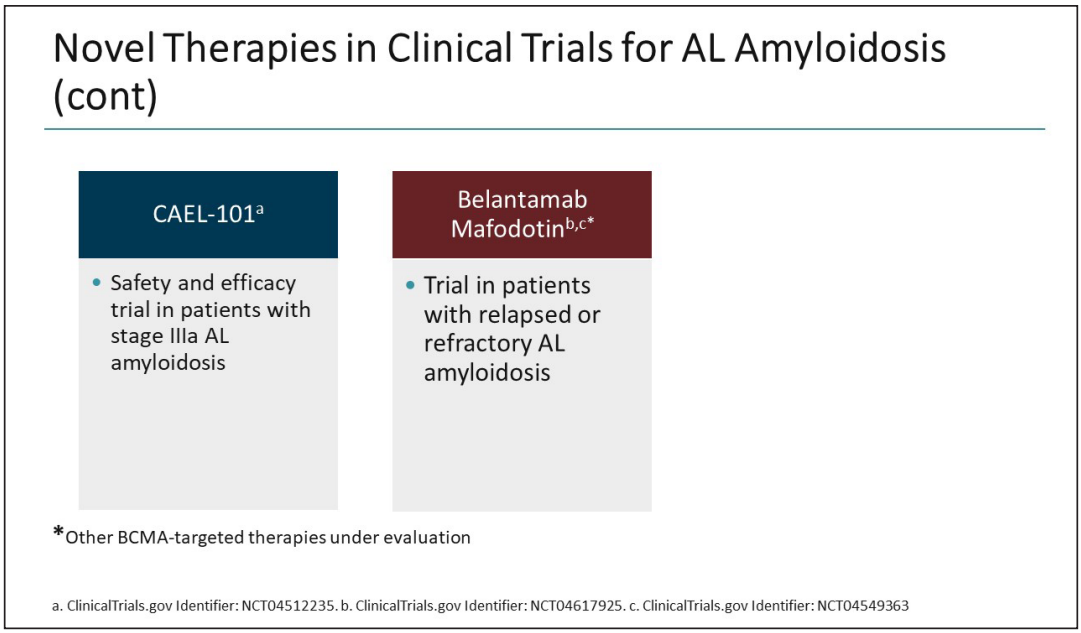
Dr Comenzo: And with respect to major organ deterioration progression free survival, you had basically a 42% less chance of having major organ deterioration if you received Dara-CyBorD. As you can see the curves were split, and this is that median follow up of about 11.5 months. And the result of the trial, Angela, was?



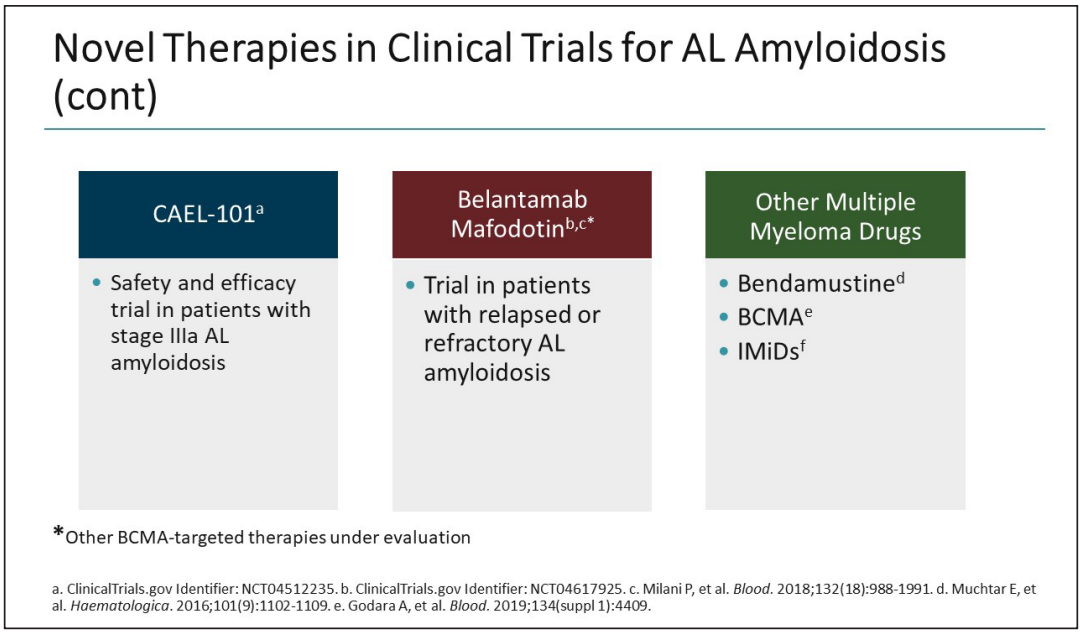
Dr Dispenzieri: FDA approval, Ray. Though, I have a question for you. What does this mean for transplant?

Dr Comenzo: I think the autologous transplant realm has been impacted by CAR T-cell therapy in lymphoma and now is being impacted by Dara-CyBorD in AL amyloidosis and also just this week by the approval of Ide-Cel for multiple myeloma. So I do think transplant remains, of those 3 diagnoses -- myeloma, AL, and lymphoma -- in some respects, transplant remains a major modality in AL, given the fact that long-term survival is present in the transplant population.

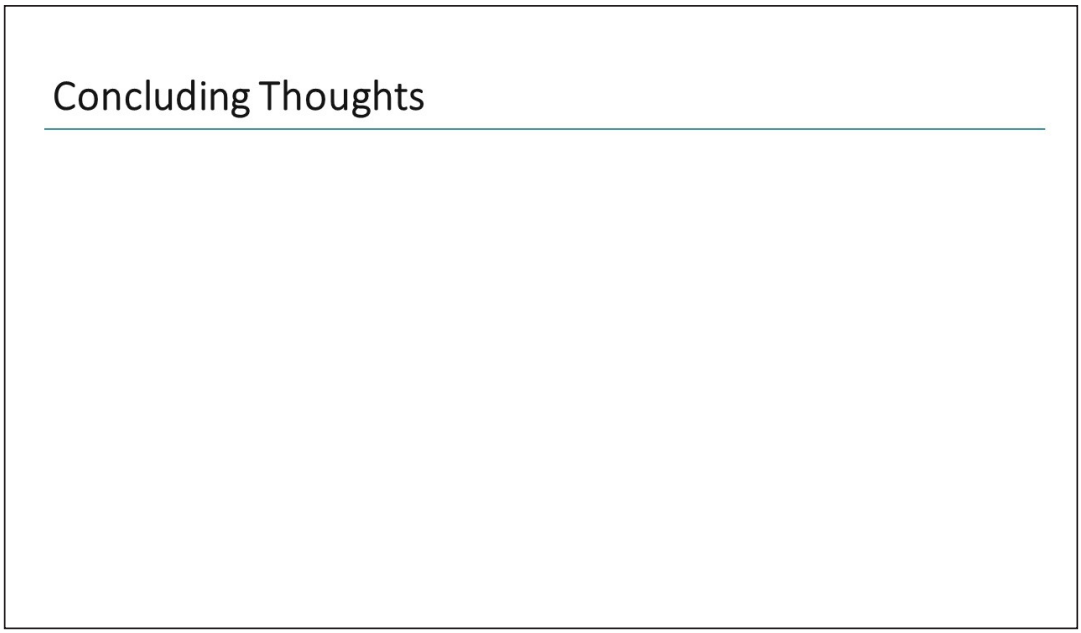
Dr Dispenzieri: And again there are some trials ongoing at this point, trying some of the more novel therapies. There's interest in using some of the new myeloma-type drugs, we have belantamab mafodotin, there's obviously the CAEL-101 trial ongoing, which is basically trying to help the body resorb the amyloid more quickly, so there's excitement around that and those are very advanced patients that they're tacking. And there are other drugs that we've tested, bendamustine. The IMiDs, again, are out there but not always really our first choice, although we love them to death in multiple myeloma, right? But in the AL patients, not so much.



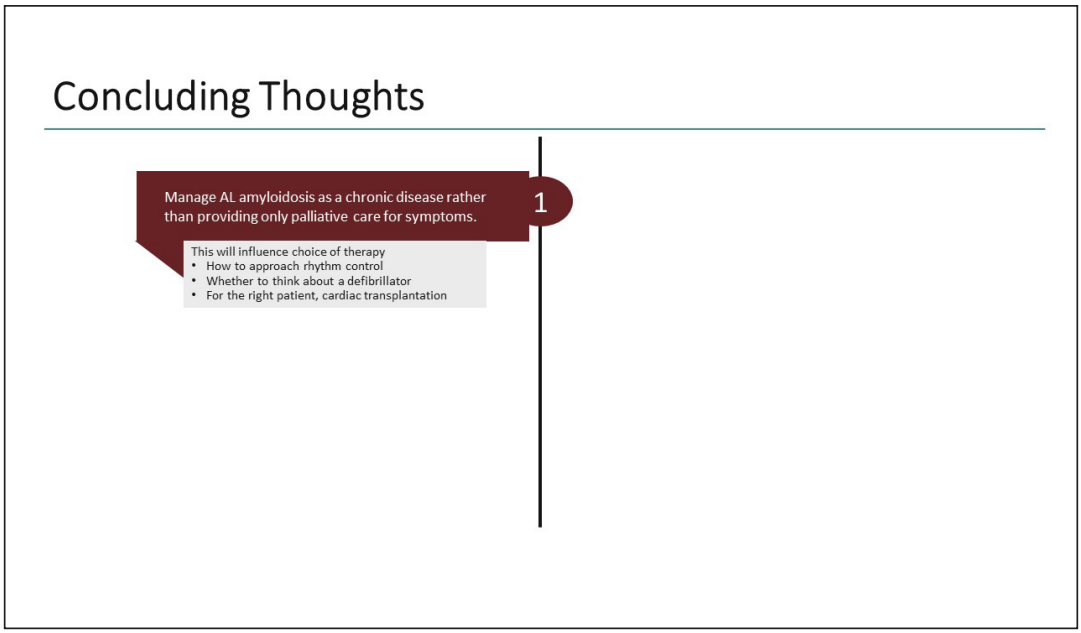
Dr Comenzo: So we've treated several patients with belantamab mafodotin, and it's a challenging drug because of the risk of keratopathy, which is clouding of the cornea. It's a reversible side effect, but patients have to be evaluated before each dose, every 3 weeks. And the 2 patients that we've treated responded dramatically well.



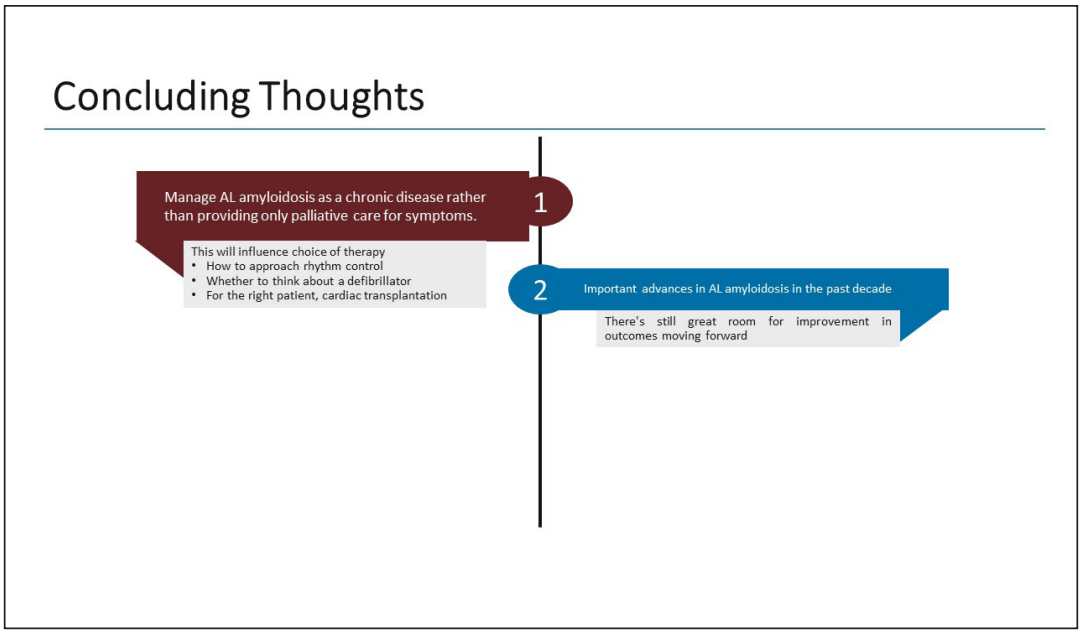
Dr Comenzo: There are other BCMA-related therapies that may be of value in AL patients. We're very hopeful in that area. So it's a very promising horizon overall, I believe, for AL amyloid, but we'll have to proceed with the clinical trials and the guidance of pharma and the FDA.



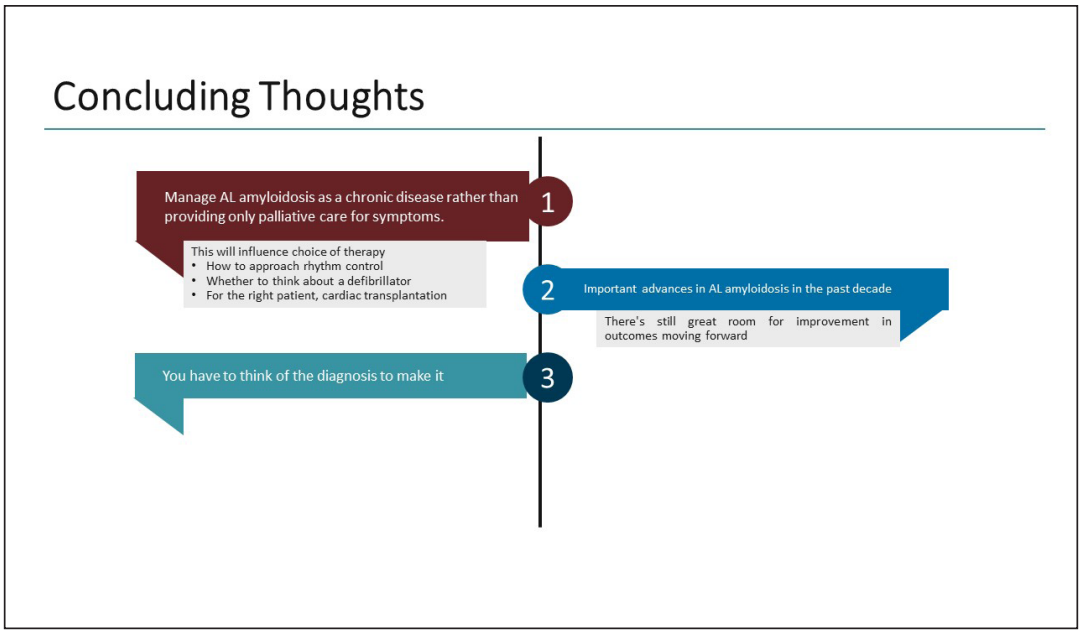
Dr Comenzo: So, it's been a fascinating discussion. I think the experts have sounded in on many, many challenges that doctors and other clinicians and patients and their families can confront as they try to make the diagnosis and also provide support and therapy. Ron, Angela, what final thoughts would you like to leave with our wonderful, wonderful audience?



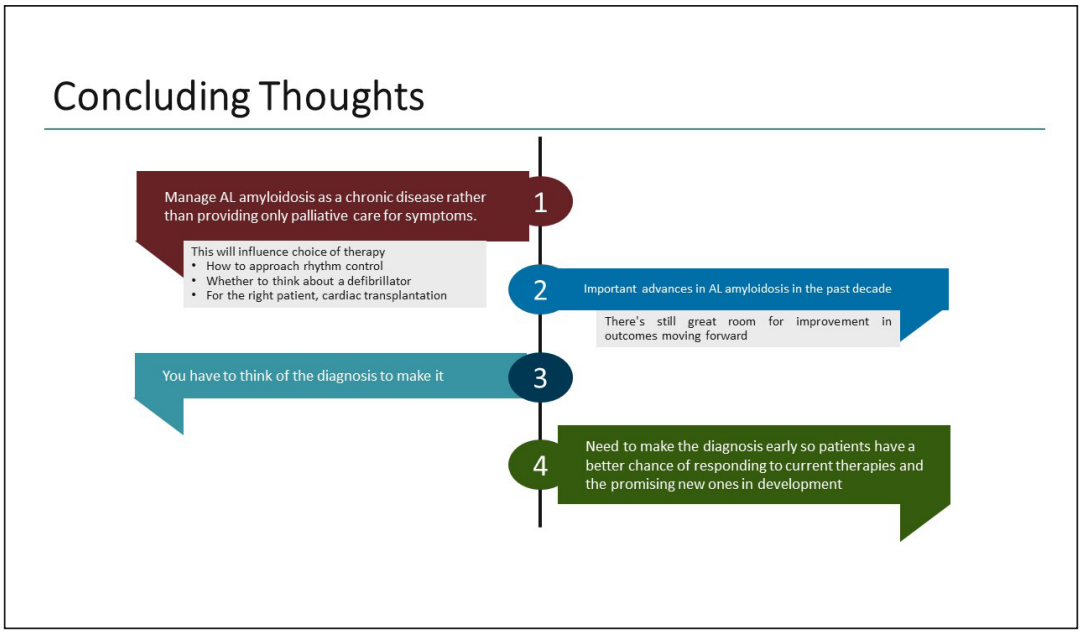
Dr Witteles: Well thanks, Ray. I guess, I'd say from my perspective, 2 things. One, as a cardiologist is that it's time often to think of this now as managing a patient with a chronic disease, not one of just palliating symptoms and that can impact your choice of therapies, how you're going to approach rhythm controls, whether you're going to think about defibrillators, and even for the right patient, start thinking about cardiac transplantation.



Dr Witteles: The second thing I'd say is just that this is an exceptionally exciting time in amyloidosis. ATTR amyloidosis has gotten a lot of attention recently because of the big advances in diagnosis and therapy, but I'd say that the advances in AL amyloidosis in the last decade have really been no less incredible and no less impactful. So there's still great room for improvement in outcomes moving forward, but there's really never been a more exciting time in the field. And thanks for having me today.



Dr Dispenzieri: I would echo that. I think the 1 thing, I can't say it enough, is you have to think of the diagnosis to make it, because there are patients that really, despite really good plasma cell-directed therapy, the horse is so far out of the barn, that a majority of a small fraction will... It's hard to help them. So we need to make that diagnosis.



And there is just so much excitement. The therapies that are currently available, the really interesting work going on in myeloma with type-specific T cells and CAR Ts. At some point, I think these other more exciting or novel types of immunotherapy will be accessible for our patients as well with AL. And so make the diagnosis and lots of hope.

Dr Comenzo: Angela, thank you. Ron, thank you. This has been a wonderful, wonderful discussion.

And I especially want to thank our audience. Thank you for participating in this discussion about AL amyloidosis and the improvements in therapy. Please answer the questions that follow, complete the evaluation of the course, and keep your eyes open for cases as they come through your clinic.

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Abbreviations

ACE-I = angiotensin-converting enzyme inhibitor

AE = adverse event

AL = amyloid light-chain

ARB = angiotensin II receptor blocker

ATTR = amyloid transthyretin

BCD = bortezomib, cyclophosphamide, and dexamethasone

BCMA = B-cell maturation antigen

BM = bone marrow

BMBx = bone marrow biopsy and aspiration

BMDex = bortezomib plus melphalan and dexamethasone

BNP = B-type natriuretic peptide

CAR = chimeric antigen receptor

CHF = congestive heart failure

CR = complete response

CyBorD = cyclophosphamide, bortezomib, and dexamethasone

DARA = daratumumab

Dex = dexamethasone

DGE = dynamic glucose enhanced

DPD = 3,3-diphosphono-1,2-propanodicarboxylic acid

eGFR = estimated glomerular filtration rate

FLC = free light chain

GI = gastrointestinal

H&E = hematoxylin and eosin

ICD = implantable cardioverter-defibrillator

IDE-CEL = idecabtagene vicleucel

IMiD = immunomodulatory imide drug

LC = liquid chromatography

LVH = left ventricular hypertrophy

MALToma = lymphoma involving mucosa-associated lymphoid tissue

MASS-FIX = matrix-assisted laser desorption ionization time-of-flight mass-spectrometry

MGUS = monoclonal gammopathy of undetermined significance

MOD-PFS = major organ deterioration progression-free survival

MRD = minimal residual disease

MRI = magnetic resonance imaging

NT-proBNP = N-terminal pro–B-type natriuretic peptide

NYHA = New York Heart Association

PYP = pyrophosphate

SC = subcutaneous

SIFE = serum immunofixation test

SPIE = serum protein electrophoresis with immunofixation

UIFE = urine immunofixation test

UPIE = urine protein electrophoresis with immunofixation

VGPR = very good partial response

VT = ventricular tachycardia