PREM SOMAN: Hello, everybody. The numerous proteins in our bodies are composed of amino acids linked by carboxyl bonds. These chains of amino acids in the process of forming proteins undergo sequential folding into primary, secondary, tertiary, and sometimes quaternary structures. This complex structural conformation is important for the stability and function of the protein.

Amyloidosis is a protein misfolding disease where native proteins misfold. They tend to clump together into fibers of amyloid. Now under the microscope, all amyloid look the same and are composed of a secondary structure composed of cross beta pleated sheets. This secondary structure conformation gives amyloid its characteristic imaging properties. For example, when stained with Congo red and observed under polarizing microscopy, it exhibits a green birefringence.

So irrespective of the protein of origin, all amyloid looks the same. Now cardiac amyloidosis is composed usually of one of two varieties. More than 95% of cardiac amyloidosis is derived either from immunoglobulin light chains, that is AL amyloidosis, or transthyretin fibrosis, which form ATTR amyloidosis.

About 5% of cardiac amyloid is composed of rare varieties that are shown here. Now TTR cardiac amyloidosis is not a rare disease. Recent data suggests that about 13% of patients with heart failure with preserved ejection fraction with left ventricular hypertrophy may have TTR cardiac amyloidosis. And in certain, it is also prevalent in certain well-defined populations such as patients with low gradient severe aortic stenosis, of whom up to 12% may have cardiac amyloidosis

AL amyloidosis is a plasma cell dyscrasia resulting in the unregulated proliferation of a single clone of SPAAR plasma cells, resulting in the excess production of immunoglobulin light chains. Since this is a monoclonal disease, the light chains are either kappa or lambda and these excess light chains produce amyloid and are deposited in many different organs of the body, producing a systemic disease as you know, if not treated and if not diagnosed and treated promptly, this is often a fatal disease.

Transthyretin, the carrier of thyroxine or retinol or vitamin A is a protein that is produced in the liver. Misfolded transthyretin leads to ATTR amyloidosis, which can exist in two varieties. The hereditary of variant form of TTR amyloidosis is inherited as an autosomal dominant disease and can manifest either as hereditary amyloid polyneuropathy, hereditary amyloid cardiomyopathy, or as a phenotype that exhibits a combination of both of these types.

Wild-type TTR exists without an underlying gene mutation and is primarily a cardiomyopathy. Although we are increasingly recognizing the involvement of other areas of the body, such as carpal tunnel and the spinal cord tendons in the vertebral column. The tendons in the vertebral column. Now here are listed some of the genotypes and the corresponding phenotypes of TTR mutations. Now the TTR gene resides on the long arm of chromosome 18.

Here is shown the conventional nomenclature of TTR gene mutations. For example, about 4% of the African-American population in the United States carries the V122 isolation mutation. Now this means that there is substitution of valine by isolation at the 122nd position of this chromosome.

More recently, the A20 amino acid signaling peptide that exists on this chromosome is also being included in the nomenclature. So you will sometimes encounter the V122 isolation mutation being referred to as the P144 isolation mutation. The second most common mutation in the United States is the T60, a mutation of the PT80 mutation, which, for example, is prevalent in the Irish population in Central Pennsylvania. This is also known as the appellation mutation and originated historically from Donegal in Ireland.

So most of these mutations are associated with specific and predictable phenotypes. For example, these mutations are associated with the cardiac phenotype and these mutations are generally associated with the neurological phenotype. When does one suspect cardiac amyloidosis? Well, let me start by saying that this is a diagnosis that requires a very high degree of suspicion. Recent data suggests that when patients present, a physician's diagnosis is generally delayed by two to three years after the initial presentation. So it's important to recognize what are called the red flag symptoms of cardiac amyloidosis, which are shown here.

Now in systemic amyloidosis, there are some very typical features, such as macroglassia. So shown here is a picture of a patient with macroglassier showing the indentations, the tongue indentations, because of the macroglassier. Perio orbital petichea is almost pathognomonic of amyloidosis and amyloid deposits can be seen in multiple parts of the body. With wild-type amyloidosis, tendon rupture is a very typical finding and a bicep tendon rupture should immediately make one think of wild-type cardiac amyloidosis.

We are now recognizing that a number of patients with bilateral carpal tunnel release go on to develop cardiac amyloidosis. And it is not at all common to identify a history of bilateral carpal tunnel release, which was performed seven to 10 years prior to the diagnosis of cardiac amyloidosis. And so also, spinal stenosis.

This diagram is here just to show the protean manifestations of amyloidosis involving multiple systems. Again, emphasizing the fact that a very high degree of suspicion is required. Also orthostatic hypotension is a red flag symptom. For example, in patients who have required antihypertensive therapy for a long time and suddenly start becoming hypertensive on antihypertensive therapy, if they have an echo showing LVH, one should suspect cardiac amyloidosis.

Similarly, nonspecific GI symptoms, peripheral sensory, motor neuropathy, sexual dysfunction, and so on and so forth. So the clinical alerts for amyloidosis, things that we should be very specifically looking for, particularly in patients with LVH are bilateral carpal tunnel, relief in a male with HFpEF, and as I mentioned, usually occurs five to seven years prior to the diagnosis, unexplained left ventricular hypertrophy, particularly if the ECG shows a disproportionately lower voltage.

It is important to remember that a new diagnosis of hypertrophic cardiomyopathy, especially when it occurs in the older patients, for example, patients older than 60 years of age, amyloid is probably more common in that situation than hypertrophic cardiomyopathy itself. It's important to remember that asymmetrical left ventricular thickening is not uncommon in cardiac amyloidosis. Orthostatic hypotension and unexplained neuropathic pain, as I mentioned.

And I also want to emphasize here that unlike the notion that prevailed years ago, wild-type ATTR is not exclusively a disease of men, and even in our own database, about 8% to 10% of patients with proven wild-type ATTR are women. Now let's look at some imaging and other clinical pointers to cardiac amyloidosis. Now the classic ECG in amyloid is ingrained in our heads and often appears in multiple choice questions at various levels of our training and beyond.

And the classic EKG is a low voltage EKG in a patient with very thick ventricles. However, I will caution you here by saying that a low voltage EKG is uncommon in critical doses and exists in only about 25% of patients with wild-type ATTR, which is much more common and in about 50% of patients with AL amyloidosis. So if one relies on the presence of a low voltage ECG to make a diagnosis of amyloidosis, you will miss most patients, although the presence of a low voltage ECG in the context of the ventricles is very highly suggestive and quite specific for cardiac amyloidosis.

The most common ECG patterns that are encountered are the pseudo infarct pattern, as is shown here in the anterior lead, and many patients have atrioventricular blocks. So the combination of the pseudo infarction pattern and AV blocks in the context of clinical suspicion or a suggestive echo should increase, should alert the physician to the possibility of cardiac amyloidosis. It is also important to remember that 10% to 20% of patients have overt LVH on the ECG. So the presence of overt LVH on the ECG does not exclude AL amyloidosis.

More important than the low voltage EEG is the concept of the voltage to LV thickness discordance, and there are a number of scores to quantify that. So more commonly than absolute low voltage, what is encountered is this discordance between LV thickness and voltage. Now the echo is often the first test from which a diagnosis. If amyloidosis is suspected, here is shown a classical amyloid echo with thick ventricles, which is often the finding that triggers a suspicion. The other things that make amyloid likely in the context of the ventricles are a pericardial effusion, shown here. A small pericardial effusion and a thick into atrial septum. The normal intranasal septum is about six to eight millimeters thick.

And the combination of the ventricles with a pericardial effusion and thickened atrial septum makes the suspicion of an infiltrate of cardiomyopathy very high, especially in the context of an ECG that shows conduction blocks. Yes. The combination of these echo features with an ECG with conduction abnormalities should make the diagnosis of amyloid very high on the cards.

The other eco features that are prevalent are RV thickness, increased RV thickness, thick valves, and biatrial enlargement, which is also seen in atrial fibrillation. Note however, again, that asymmetrical septal hypertrophy can occur in patients with amyloidosis. And in a patient who is older than 60 years, a new diagnosis of hypertrophic cardiomyopathy should trigger a suspicion of cardiac amyloidosis.

A more recent finding that increases the suspicion of cardiac amyloidosis is a longitudinal strain abnormality that space the apex, as is shown here. As the myocardium contracts in two directions, there is radial contraction which is usually reflected by the ejection fraction, but also longitudinal contraction and we now know that longitudinal contraction becomes abnormal much earlier than radial contraction, which is why longitudinal straight abnormalities are a much more sensitive marker of LVH dysfunction than ejection fraction itself.

Now in amyloid, there is this unique pattern of longitudinal strain abnormality that spares the apex that is quite sensitive for the detection of cardiac amyloidosis. So if it's absent it reduces the probability of cardiac amyloidosis but its presence is not specific for cardiac amyloidosis. And it can be seen in other conditions such as LVH associated with chronic kidney disease and aortic stenosis.

So it is good as a sort of a screening tool, although it's not perfect. And the diagnosis of amyloidosis cannot be completely excluded or confirmed by the presence or absence of the longitudinal strain abnormality. Cardiac MRI is very useful and shows all the morphological features that are seen on echocardiography. In addition, certain unique abnormalities and gadolinium kind of resulting in an inability to nail the myocardium are thought to be very suggestive of cardiac amyloidosis. What is most commonly seen is diffuse segmental cardiol enhancement by late gadolinium, very high T1 values and very high ECV.

The higher the T1 value and the greater the ECV, more suggestive, that is, for cardiac amyloidosis. This is data from our colleagues here, showing that a high ECV portends a particularly bad prognosis in patients with cardiac amyloidosis. Now, as many of you might know, cardiac [INAUDIBLE] with the bone seeking traces and what is used in the United States is technician pyrophosphate, has pretty much transformed the field of cardiac amyloidosis.

Now before it was recognized that PYP scanning has an extraordinarily high diagnostic accuracy, one needed a cardiac biopsy to confirm a diagnosis of cardiac amyloidosis. This led to only the patients with the highest suspicion being tested. And so it looks like we missed a great many number of cases with cardiac amyloidosis. The ability to make a non invasive confirmed diagnosis of cardiac amyloidosis has unmasked a hitherto completely unrecognized prevalence of cardiac amyloidosis in the community.

Here are a classic examples of planar imaging for the patient without cardiac amyloidosis. And you don't see the cardiac silhouette at all. Here's a patient with cardiac amyloidosis showing very avid uptake of the tracer by the myocardium. Now although much of the data-- and I will not go into the particulars here because of time constraints-- although most of the data with which PYP scanning was introduced was based on planar imaging, I think today it's fair to say that the diagnostic standard has to be the demonstration of diffuse uptake of the tracer on SPECT imaging.

This is really important because fact is critical to differentiate a positive planar scan due to persistence of blood pull in the cavity as opposed to a truly positive planar scan, because of diffuse uptake by the myocardium. So the diagnosis has to be based on the demonstration of diffuse myocardial uptake of the tracer on SPECT. Now I often say that a positive PYP scan looks very much like a normal myocardial perfusion scan with a technetium tracer such as sestamibi or tetraphosphate.

And so if a PYP scan looks like a normal myocardial perfusion scan, then it is unequivocally positive. Now this is the now famous paper that established the high diagnostic accuracy of PYP. This is a multinational, multicenter paper. And shown here are the sensitivity and specificity figures. As you can see, the technique has a very high sensitivity, but what I really want to emphasize on this slide here, that the very high specificity is obtained when the PYP scan is interpreted in the context of normal serum studies to exclude AL amyloidosis.

Now I cannot emphasize this point enough. And this is because some patients with AL amyloidosis may show mild PYP uptake on PYP scintigraphy. Now as I don't have to emphasize to this audience here how critical it is to differentiate AL from ATTR amyloidosis. And so PYP centography always, always has to be interpreted in the context of negative serum studies for AL.

Now the complement of tests that exclude AL amyloidosis doses with the greatest negative predictive value are the following-- serum, free light chains, and the kappa-lambda ratio, plus urine and serum immunofixation electrophoresis. So it's electrophoresis with immunofixation. The traditional protein electrophoresis, both of the serum and urine, the SPEP and UPEP, are not sensitive enough to be used as a screening test for AL amyloidosis, so when you order serum studies to exclude AL, please order serum free light chains and the ratio, and serum and urine immunofixation electrophoresis.

Now about 99% of patients with either AL amyloidosis, primary AL amyloidosis, or amyloidosis as a result of multiple myeloma. But 99% of patients will have an abnormality in one of these tests. So the complement of tests is very useful and has a high negative predictive value for excluding AL amyloidosis.

So to emphasize this again, the definitive diagnosis of a ATTR cardiomyopathy is established by a combination of a positive PYP and a negative monoclonal and a complement of tests that exclude a monoclonal process in the serum. Of course, this can also be done by tissue biopsy of the heart in ATTR [INAUDIBLE] amyloidosis, and many other organs in AL amyloidosis. And tissue typing, in the most specific method, is laser dissection with mass spectrometry.

Now with the advent of PYP centography and by using PYP studies and serum studies in combination, we are now sending only the minority of patients for biopsies. And again, it's very critical to differentiate ATTR from AL amyloidosis, which is why the serum studies are very, very important.

So in a patient with clinical suspicion, how do we start? The clinical suspicion is for ATTR amyloidosis. For example, if it's a proband of an index patient with hereditary ATTR amyloidosis, or if it's, for example, an elderly gentleman with bilateral carpal tunnel syndrome and echo features suggestive of amyloidosis, in this patient the most expeditious sequence is probably to start with a pyrophosphate scan with serum studies and if this is positive, genetic testing to determine whether this is the hereditary or wild-type variety.

If AL is the primary suspicion, for example, if the patient is younger or has systemic findings suggestive of AL amyloidosis, or if the differential is broad, we start with a serum. I'm sorry. We start with a CMR and the CMR is suggested for amyloid. We do serum studies. Now when the serum studies are negative, we go down the PYP pathway and a positive CMR, a CMR that's very suggestive of amyloid with negative serum studies and a positive PYP, then obviates the need for a tissue biopsy.

If the serum studies are positive and if the CMR is very suggestive, we almost always need a bone marrow biopsy and tissue, and at this point a hematologist mandatorily becomes involved. For the sake of completion here. I will say that the diagnosis of AL comprises of two components. One is the demonstration of a monoclonal proliferation of plasma cells, and this is done by serum studies that indicate a high kappa or lambda level and a high ratio and the demonstration of increased plasma cells on the bone marrow.

And the second component is the demonstration of tissue deposition of amyloid. And this is done by tissue biopsy and Congo Red training followed by immunohistochemistry or with mass spectrometry. So the diagnosis of AL amyloidosis consists of these two components.

Now here are shown the sensitivity of other tissues for the diagnosis of amyloidosis. For example, the fat pad aspirate has a 70% sensitivity for AL and only at 20% or lower sensitivity for wild-type ATTR, and a slightly higher sensitivity for hereditary ATTR. So not a highly sensitive technique. In general, if you think of amyloid and a particular organ is obviously involved.

For example, if you think amyloid and the myocardium is involved, it is probably most expeditious to biopsy that particular organ to come to-- make a specific diagnosis.

Now a little bit about TTR therapies. Pharmacotherapy in TTR amyloidosis has had some extraordinarily exciting developments. And to understand this, let me just go over the structure of an amyloid fiber. Now here is the structure of an ATTR amyloid fibril shown here. As I mentioned, TTR, or transthyretin, is a carrier of thyroxine and vitamin A. It is the same compound as prealbumin. It was called prealbumin because on serum electrophoresis it moves ahead of albumin and it's the same pre albumin that we test to determine a patient's nutritional status.

As most of pre albumin is produced by the liver, and small amounts are produced by the choroid plexus in the brain and the retinal pigment epithelium. Now TTR is a tretramer, so it is composed of four component monomers. And these monomers are held together by thyroxine binding sites. There are two thyroxine binding sites for each TTR tetramer. It isn't entirely clear whether the process that initiates the formation of the amyloid fibril is the dissociation of the tetramer into its constituent monomers, or it is the cleavage by some proteolytic process of this tetramer into its constituent monomers.

Nevertheless, once the tetramer dissociates the individual monomers misfold. They become aggregation prone and they clump together to form the classic amyloid fibril. Now when there is a mutation that destabilizes the tetramer, are about 120 gene mutations that are known to destabilize the tetramer and produce TTR amyloidosis.

The mechanism of TTR dissociation into its monomers with wild-type ATTR is not exactly known. Now the approaches to pharmacotherapy and the approaches to therapy of TTR amyloidosis has followed the lifespan, if you will, of ATTR amyloid fibril from its production into the liver, to its dissociation into its constituent monomers, and then clumping and the formation of the amyloid fibril.

So the first step, of course, would be suppression of TTR synthesis, and there are a number of approaches that have been used. For example, for hereditary ATTR, one could transplant the abnormal liver with a normal liver and therefore result in the production of not variant TTR, but the normal TTR that is genotypically normal and therefore most stable.

Now liver transplantation has gone out of vogue and was anyway performed much more outside the US and for neuropathy than within the US or for cardiomyopathy. 10 year survival is very good, but it's important to note that retarding the production or stopping the production of abnormal TTR retards the progression of disease and as of now, there is no evidence that it reverses the disease process based on TTR that is already deposited in the organs.

It's also important to note that it is now very well recognized that when patients have liver transplantation, cardiomyopathy can progress and continue to progress because of the seeding of wild-type ATTR fibrils onto the small amounts of mutant TTR or variant TTR that existed in the heart before liver transplantation. So cardiomyopathy can progress not because of familial or hereditary ATTR, but because of the seeding of wild-type TTR fibrils.

The second approach is being one of the most exciting developments in all of pharmacotherapy, and that is to use RNA silencing drugs to inhibit the synthesis of TTR. Now in a very simplistic sort of way you know that the information in the DNA is transcribed by the RNA and then translated into protein synthesis by RNA. And the RNA silencing mechanisms inhibit both the transcription and translation processes and thereby inhibit the production of TTR, of both wild-type and variant TTR by the DNA.

Now there are two different types of compounds that have been developed for RNA silencing. One is the antisense oligonucleotides. The other are small interfering RNA or SiRNAs. They both act in slightly different mechanisms but both result in the profound reduction in TTR. translation, and they knock down both wild-type and variant TTR by 70% to 80%.

Many of you might know that the Nobel Prize for medicine in 2006 went to Andrew Fire and Craig Mello for the development of small interfering RNA synthetic small interfering RNA, based on which they were able to silence specific gene mechanisms in *c. elegans.* We have now two RNA silencing therapies that are approved, but only for hereditary transthyretin neuropathy. Inotersen was the first of these.

I'm sorry, Patisiran was the first approved RNA silencing agent and this is small interfering RNA and the second to be approved was Inotersen, which is an antisense oligonucleotide. As I said, they're both approved only for hereditary transthyretin polyneuropathy, but can be given to patients with hereditary cardiomyopathy if they also have hereditary polyneuropathy and they lock down TTR by about 70% to 80% and pre albumin levels actually fall therefore during therapy with these agents.

Another very, very interesting development, and this is hot off the press, has been the demonstration for the first time in humans of gene editing by using the CRISPR Cas9 mechanisms and in six patients with hereditary amyloid polyneuropathy, the successful knockdown of TTR was shown resulting as you can see in more than 85% knockdown of TTR. Only in these six patients and of course, as TTR levels fall prealbumin levels also fall.

So those are the existing and the established and experimental mechanisms for reducing the production of TTR. The second approach is to stabilize the tetramer so that it does not dissociate into its constituent monomers. Here again, is a diagrammatic representation of the monomer. I showed you the thyroxine binding sites. The TTR tetramer also binds to retinol binding proteins, which is what allows it to carry vitamin A. Now it's important to remember that the retinol binding protein, which is not bound to TTR, consists of very small molecules, and if they are not bound to TTR they're rapidly excreted by the liver.

So when you knock down TTR it is important to supplement vitamin A. I made a mistake in these. If they are not bound-- unbound retinol binding protein is excreted by the kidneys, not by the liver. Now shown on this diagram are the more prevalent gene mutations that produce either thermodynamic or genetic instability in the TTR tetramer leading to its dissociation.

Another very interesting finding that led to some pharmacotherapeutic developments, was the recognition of certain gene mutations as for example, the T119 mutation, that, as opposed to destabilizing the TTR tetramer, actually stabilized it. And the finding was serendipitous. When it was discovered that certain patients with the V30M mutation, when they are co heterozygous for the T119 mutation, did not develop clinical disease.

And that is what led to the recognition that the T119 mutation actually stabilizes the TTR tetramer, and therefore is a rescue mutation. Now the agents that are currently available as stabilizers for TTR amyloidosis are Diflunisal, which is just a NSAID that has been around for a very long time and is actually quite a potent TTR stabilizer. Tafamidis, which is the Pfizer drug that was approved several months ago amid much fanfare and is currently the only approved therapy for TTR amyloidosis, and AG10, which is an experimental drug that looks like it's a very potent stabilizer of TTR and is currently undergoing Phase III trials.

Now Diflunisal and Tifamidis bind to the T4 sites, and that is the mechanism by which they stabilized TTR. AG10 actually mimics the binding properties that are produced by the T119 mutation and therefore mimics the action of the T119 mutation in its mechanism of stabilizing TTR. There is not a lot of data on the use of solid cardiomyopathy being an NSAID. It has all the side effects of NSAIDs, including sodium and water retention and renal dysfunction and GI bleeds. It's a difficult agent to use.

We have used it in some patients who are unable to get Tifamidis, primarily because of cost considerations, and patients who do not have overt severe heart failure. And these patients do tolerate Diflunisal surprisingly well, and some of them have been on it for several months. Now Tifamidis, this is the ATTR ACT study that was published in the New England Journal of Medicine in 2018. Tifamidis, families in this large study, was shown to reduce both all cause mortality and cardiovascular hospitalizations in ATTR ACT.

I often think of Tifamidis as the first drug that was shown to have this dramatic mortality reduction in patients with HFpEF, which is otherwise an area where we've not had a lot of pharmacotherapeutic success. Tifamidis showed over a four year period of follow up a 33% mortality reduction resulting in the number needed to treat of about 7 to 8. And also a 32% reduction in CV hospitalization.

Now it took about 18 months for the mortality and CV hospitalization effects Tifamidis to become manifest, and I point this out because it emphasizes the fact that it is important to diagnose and treat patients with TTR amyloidosis early. Now I will tell you here that in the pre-Tifamidis era, ATTR, wild-type ATTR is not as benign a disease as we thought it was, and most patients, the survival of patients with established ATTR wild-type amyloidosis is about three to five years after the diagnosis.

Now because of the mechanism of action of stabilizers, they do not reduce the production of TTR, but rather they stabilize both wild-type and variant TTR, and because of that the pre albumin levels rise. So it is reasonable to say that this mechanism of therapy is probably more physiological than the severe reduction in TTR levels that are seen with the RNA suppressive therapies.

This is a slide from Dr. Matt Mora from Columbia who ran the ATTR ACT trial, again emphasizing that the maximum mortality benefit was in patients with early disease. So the earlier you can diagnose ATTR amyloidosis and treat it, the greater the benefit to the patient. This is just one slide. This are preclinical studies of AG10 showing here that these are Western blot studies showing the amount of stable TTR in the presence of Tifamidis and AG10 and a non stabilizer, and you see here that AG10 is a very potent stabilizer of TTR and that led to the attribute cardiomyopathy trial, which is the Phase III trial that is currently ongoing.

And finally, so we started off with suppression of TTR synthesis and then went on to TTR stabilization, and finally there are a number of agents that are being tried with the aim of reabsorbing, absorbing, or removing TTR fibrils that have already been deposited. Some of these studies are undergoing clinical trials, but compared to TTR suppression and TTR stabilization, this area of pharmacotherapy has not had a great deal of success, or relatively small amount of success and we don't have powerful agents in this class of therapy.

So to summarize, for wild-type ATTR, which is by and far the largest group of patients that we're all likely to encounter, Tifamidis is approved and Diflunisal can be used in patients who can tolerate it if they cannot afford Tifamidis. Now, Tifamidis cost about $250,000 a year. Most patients are able to obtain Tifamidis at lower costs based on co-pay assistance programs and so on and so forth. But it is a very expensive drug.

For hereditary ATTR, if they have neuropathy one can use either the antisense oligonucleotide or the small interfering RNA therapy for suppressing TTR. Of course, both Tifamidis and Diflunisal can be used in addition if they have cardiomyopathy. We don't have a lot of data on combination therapy, but of course that is a question that is very logical, but we don't have answers as to the advantage of combination therapies, and of course cost would be a very huge consideration.

Now the RNA silencing agents, both Patisiran and Inotersen, are being tried in wild-type cardiomyopathy and several clinical trials are ongoing as we speak. A brief word about heart failure management, there are some unique considerations in cardiac patients. In patients with cardiac amyloidosis, Digoxin and calcium blockers are not well tolerated at all and should be stopped because they often produce conduction blocks or induce progression of conduction blocks and are negatively isotropic. Beta blockers are best stopped and most patients feel much better off beta blockers than on beta blockers, and this is because of the severe restrictive physiology.

Patients are dependent on heart rate for their cardiac output and slowing them down with beta blockers actually has an unfavorable effect on cardiac hemodynamics. Occasionally, beta blockers, we do leave them on for rate control in patients with atrial fibrillation because a large number of these patients do have atrial fibrillation. ACE inhibitors, again, I leave them on if they are tolerated, but many patients, because of hypertension, do not tolerate ACE inhibitors, even if they have a low ejection fraction, which about 30 to 40 patients with ATTR amyloidosis will have.

So important to remember here that guideline-based therapy for heart failure is often poorly tolerated in patients with cardiac amyloidosis, and diuretics including spironolactone are usually the mainstay of therapy. In my own practice, I use a lot of spironolactone. Although it has not been specifically tested for amyloid, one could extrapolate that its anti fibrotic effects might have some beneficial effects in these patients, in whom most of the other standard therapy for heart failure are very poorly tolerated.

I want to emphasize that one should have a very low threshold for anticoagulation in these patients. The combination of atrial fibrillation and ATTR cardiac amyloidosis increases the risk for stroke exponentially, and any atrial fibrillation in patients with cardiac amyloidosis should be a basis for anticoagulation. And our own data shows that the stroke risk is not well protected by CHADS scores in these patients.

So any evidence of atrial fibrillation, and of course there are now, some debate as to whether patients with evidence of mechanical atrial dysfunction-- I showed you the pictures of CMR studies and in echo studies, the atria usually very enlarged and there is usually atrial mechanical dysfunction-- if we can quantify that, there may be a basis for anticoagulation even in the absence of atrial fibrillation in the future.

As of now, any atrial fibrillation, however short lived, irrespective of the CHADSVASC score should be a basis for anticoagulation of these patients. So on my final slide, I will leave you with perhaps the most important take-home message here, and that is think of cardiac amyloidosis. This is the first step in making a diagnosis.

This is the email of my assistant, Rebecca Conley, who schedules patients for our cardiac amyloidosis center. I would say that the most critical step is making the diagnosis and differentiating ATTR from AL amyloidosis, which can be quite nuanced and tricky in many of these patients. And that's something that we can do for you. Our patients have access to all the latest clinical trials and of course all the available therapy. So thank you very much.