Transthyretin Cardiac Amyloidosis:
Frequently Asked Questions
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Transthyretin amyloid cardiomyopathy (ATTR-CM) is a life-threatening, progressive, infiltrative disease caused by build-up of transthyretin amyloid fibrils in the heart. This condition is often overlooked as a common cause of heart failure. ATTR-CM can now be treated but an early and accurate diagnosis is critical to improving patient outcomes.

Identifying Patients with Suspected Cardiac Amyloidosis

Key Points Regarding Cardiac Amyloidosis (CA)

- ATTR can either be hereditary due to a variant TTR gene (ATTRv) or wild type (ATTRwt) seen mostly in the elderly. Genetic testing is important of diagnosing patients with ATTRv and ATTRwt.
- Hereditary TTR amyloidosis is common in certain populations including those with the transthyretin V122I (pV142I) mutation such as African Americans and Afro-Caribbean's. Polyneuropathy is commonly associated with Val30MET mutation, whereas, cardiomyopathy is associated with V122I, Leu111Met and ILE68Leu. T60A is a frequent cause of polyneuropathy and cardiomyopathy.
- Wild-type TTR amyloidosis is a frequent cause of heart failure with preserved ejection fraction (HFpEF) in older patients and is seen in patients with low flow aortic stenosis, atrial fibrillation, and settings of increased wall thickness.
- The most common symptom of ATTR-CM is heart failure.
- TTR amyloidosis symptoms vary and may mask as other common comorbid conditions requiring high-level of suspicion for diagnosis.
- TTR amyloidosis must be differentiated from light-chain amyloidosis as treatments vary.
- Screening for light chain (AL) amyloidosis requires immunofixation electrophoresis of serum and urine (SIFE/UIFE) and the quantitative serum free light chain assay (FLC).
- Echocardiography can raise the suspicion of cardiac amyloidosis and certain cardiac MR features are specific for amyloidosis; but neither can differentiate ATTR from AL amyloidosis.
- Tc-99m PYP imaging, after excluding a monoclonal process, is an accurate non-invasive method to diagnosis ATTR-CM.
- False positives studies on Tc-99m PYP planar imaging are often the result of blood pool artifact that can be distinguished from myocardial retention with single-photon emission computerized tomography (SPECT).
- Several treatments are now available to halt production or stabilize the causative protein.

The following is a list of frequently asked questions regarding ATTR, from signs and symptoms to diagnosis, treatment, and management. References are provided, when available, to further explore the issue.

Identifying Patients with Suspected Cardiac Amyloidosis

Epidemiology

The most common form of ATTRv is familial amyloid polyneuropathy (FAP) resulting from a substitution of valine for methionine at TTR position 30 (Val30MET). Prevalence in Europe is about 10/1,000,000. In some regions of Portugal, the prevalence can be as high as 1/1000 to 1/10,000. In Japan, even in endemic regions like Kuma-moto, Nagano and Ishikawa, the national prevalence estimate is 0.99/1,000,000. Another variant, Val122Ile is prevalent in 3.4% of African Americans. In developed countries, ATTRwt is likely the most common type of amyloidosis and may be the underlying diagnosis in 5–13% of patients with HFpEF.1,2
What is the prevalence of ATTR in Asians?
The global prevalence of ATTR-CM is largely unknown. A retrospective study provided an estimate of the number of patients diagnosed with ATTR-CM using a large in-hospital database in Japan over a period of 9 years resulting in 3255 (155.8 per million) and 3992 (191.1 per million) for ATTRwt and between 67 (3.2 per 1 million) and 106 (5.1 per million) patients with ATTRv in the Medical Data Vision database of 25 million records. The prevalence of transthyretin amyloid polyneuropathy has been more extensively studied in this cohort.

What percentage of patients have ATTRwt?
The true prevalence of ATTRwt is unknown. It is the most common cause of cardiac amyloidosis. Several centers find ~80% of cardiac amyloid to be ATTRwt.

Diagnostic Clues for Cardiac Amyloidosis
Are there any signs that should alert a physician to the possibility of underlying ATTR-CM?
Several experts have published “Red Flags” that should raise suspicion for ATTR-CM.

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<th>Clinical Red Flags</th>
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<td>African American cohort</td>
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<td>Heart failure (HF) with preserved ejection fraction</td>
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<td>Individuals ≥60 years</td>
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<td>Intolerance to HF medications</td>
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<td>Repeat HF hospital admissions</td>
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<td>Atrial fibrillation/bradycardia/heart block</td>
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<td>Multiple mild troponin elevations</td>
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<td>Bilateral carpal tunnel syndrome</td>
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<td>Biceps tendon rupture</td>
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<td>Orthostatic hypotension</td>
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<td>Polyneuropathy and/or dysautonomia</td>
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<td>Dysautonomia</td>
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<td>Lumbar spinal stenosis</td>
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<td>↓ Voltage on ECG in conjunction with ↑ LV wall thickness</td>
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<td>Multiple mild troponin elevations</td>
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Imaging Red Flags

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<td>Left ventricle/right ventricle wall thickening</td>
<td>LV/RV wall thickening</td>
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<td>Diastolic dysfunction</td>
<td>Atrial enlargement</td>
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<td>Reduced global longitudinal strain</td>
<td>Diffuse late gadolinium enhancement</td>
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<td>Atrial enlargement</td>
<td>Expanded extracellular volume</td>
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<td>Reduction in longitudinal strain with apical sparing (RELAPS)</td>
<td>Blood poll signal nulling prior to myocardial nulling</td>
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<td>Low-flow, low-gradient aortic stenosis</td>
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**Pathophysiology**

*What causes ATTR-CM?*

ATTR-CM is a restrictive cardiomyopathy caused by extracellular deposition of proteins in the myocardium. The proteins have an unstable structure that causes them to misfold, aggregate, and deposit as amyloid fibrils.9

**Diagnostic Algorithm**

*Is there a recommended diagnostic algorithm for cardiac amyloidosis in print?*

Several excellent publications provide a diagnostic algorithm for ATTR-CM.9-13

*What diagnostic algorithm would you use for a patient who has ischemic cardiomyopathy, supervening amyloid, and worsening heart failure?*

In a patient with ischemic heart disease, it is important to exclude active ischemia contributing to worsening heart failure. In patients with recent infarct, Tc-99m PYP scans can be positive and challenging to interpret for amyloidosis. In these mixed patients, more detailed imaging and endomyocardial biopsy may be needed to confirm cardiac amyloid deposition.

**Noncardiac Manifestations of Cardiac Amyloidosis**

*What are noncardiac manifestations of cardiac amyloidosis?*

Noncardiac signs of ATTR amyloidosis include carpal tunnel syndrome (CTS), peripheral neuropathy, biceps tendon rupture, lumbar spinal stenosis, leg weakness, eye floater, lightheadedness upon standing, poor appetite, bloating or excessive gas, and diarrhea or constipation. CTS, lumbar spinal stenosis, and biceps tendon rupture are common manifestations that may appear several years prior to onset of ATTR-CM.5,7

*How does bilateral carpal tunnel syndrome relate to cardiac amyloidosis?*

With cardiac amyloidosis there is thickening of the tenosynovial tissue and flexor retinaculum that may compress the nerve. Evidence of TTR deposits in tenosynovial tissues was demonstrated in up to 10% of patients undergoing surgery for CTS.14 There are several studies now showing that amyloid deposition in the carpal tunnel/ligaments may be seen several years prior to overt cardiac amyloidosis.14-16 The adjusted prevalence of CTS is higher among elderly men with ATTR compared with the general population. CTS is a prognostic marker in ATTR independent of cardiac involvement and precedes CA diagnosis by 5 to 9 years. The awareness of this association and time delay offers the possibility of an early pre-clinical ATTR-CM diagnosis.17

*What is the diagnostic accuracy of the apical sparing pattern cardiac amyloidosis?*

The apical sparing pattern suggests but is not totally diagnostic or 100% specific to cardiac amyloid. There are patients who do not have an apical sparing pattern of global longitudinal strain and have cardiac amyloid. It is important to address all the available clinical information when making a diagnosis.18
Do patients with aortic stenosis have cardiac amyloidosis?
ATTR-CM has been reported in patients with aortic stenosis, but its prevalence and phenotype are not known. In one study of patients with severe aortic stenosis scheduled for transcatheter aortic valve replacement, more than 15% of patients with severe aortic stenosis and as many as 29% of patients with low-flow, low-gradient aortic stenosis had associated ATTR-CM.

Should cardiac amyloidosis be suspected in patients with new normalization of blood pressure who were previously hypertensive?
Low to normal blood pressure in a previously hypertensive patient is a clinical clue to suggest possible cardiac amyloidosis. The blood pressure in patients with cardiac amyloidosis is frequently low due to a reduced cardiac output and abnormal autonomic nervous system function. Orthostatic hypotension is common, and it is a possible and easy to rule out cause for syncope in patients with cardiac amyloidosis.

What if N-terminal B-type natriuretic peptide is not available, can you still stage ATTRwt?
Troponin and estimated glomerular filtration rate (eGFR) have been shown to stage cardiac amyloidosis. The National Amyloidosis Center found troponin and eGFR to be predictive, but these biomarkers are not specific as renal function and other cardiomyopathies can also result in abnormalities of NT-pro BNP and troponin.

When do you refer someone to endomyocardial or another organ biopsy?
Although traditionally endomyocardial biopsy was required to make a diagnosis of ATTR-CM, with the emerging data on the high specificity of Tc-99m PYP imaging in select patients, endomyocardial biopsy is now reserved for challenging cases. Patients are referred for endomyocardial biopsy when the Tc-99m PYP study is equivocal or negative in a patient with typical features of amyloidosis on echo/cardiomyocardial resonance (CMR). A discordance between the imaging finding and the clinical manifestations may warrant a consideration of an endomyocardial biopsy.

Bone marrow biopsy is useful to assess plasma cell dyscrasia and to exclude AL amyloidosis in patients with abnormal serum FLC assay or abnormal SIFE/UIFE. An abdominal fat pad biopsy can diagnose ATTR in about 45% of ATTRv and in 15% of patients with ATTRwt.

What is the role of genetic testing?
Genetic testing is needed to differentiate ATTRv from ATTRwt and is recommended in all patients diagnosed with ATTR-CM. Genetic testing is highly accurate (nearly 100%) and is offered commercially by several companies.

Imaging in Cardiac Amyloidosis
When echocardiography and CMR are diagnostic for cardiac amyloidosis, is Tc-99m PYP imaging needed?
The evaluation of cardiac amyloidosis using echocardiography focuses on morphological findings related to amyloid infiltration. Thickened LV walls, (>1.2 cm) in the absence of any other plausible causes of LV hypertrophy raises concern about cardiac amyloidosis. Increased LV mass in the setting of low voltage ECG is suggestive of cardiac amyloidosis. Apical sparing is described as a typical finding in patients with cardiac amyloidosis. A definitive distinction by echocardiography of amyloidosis from hypertrophic cardiomyopathy or other causes of LV hypertrophy is difficult. Echocardiographic parameters should be combined with electrocardiographic, clinical, biomarker, and other imaging findings to maximize diagnostic accuracy.

CMR imaging offers value in two clinical scenarios: the differentiation of cardiac amyloidosis from other cardiomyopathic processes with increased wall thickening, and potentially in detection of early cardiac involvement in patients with evidence of systemic amyloidosis. A CMR evaluation for cardiac amyloidosis includes morphologic and functional assessment of the left and right ventricles and atria using cine imaging, evaluation of native T1 signal (assessed on non-contrast T1 mapping), assessment of late gadolinium enhancement (LGE) and extracellular volume (ECV) measurement. However, CMR is typically unable to definitively distinguish AL from ATTR cardiac amyloidosis.
When is cardiac MRI needed?
CMR provides information on LV mass, volumes, ejection fraction and LGE and ECV. It can be useful for initial diagnosis of heart failure. CMR provides detailed information about systolic function and cardiac structure. It can characterize tissue allowing differentiation of amyloidosis from nonamyloid wall thickening disorders. Typical findings on CMR of cardiac amyloidosis include diffuse subendocardial or transmural LGE on late gadolinium imaging with nulling of the blood pool and elevated native T1 and extracellular volume on T1 mapping sequences.11,12

Is the prognosis different when the right ventricle or atria are compromised?
There is not much data regarding RV dysfunction, partly due to continued challenges in objective assessment of RV function. Many patients with ATTR, however, have significant RV thickening and dysfunction, high right-sided pressures, and clinically predominant RV failure. RV strain will likely be an additional prognostic factor.27-29 The major concern with atrial dysfunction in amyloidosis, is the risk of atrial thrombi and resultant thromboembolism despite sinus rhythm.30 Hence, in patients with a small A wave, in the presence of evidence of atrial dysfunction by atrial strain, expert centers may consider anticoagulation, although there are no randomized control trial data to support this recommendation to reduce the risk of thromboembolism.13 More research is needed.

What causes Tc-99m PYP to be taken up in cardiac ATTR?
The precise mechanism of uptake is not known but felt to be related to a calcium mediated mechanism. It is possible that the radiotracer binds to micro calcifications, with some evidence that these are more abundant in ATTR than AL fibrils.31

Do patients with AL amyloidosis also demonstrate heart uptake of Tc-99m pyrophosphate?
Uptake of Tc-99m-PYP in AL amyloidosis is highly variable. Most AL cases show low-grade Tc-99m PYP uptake. However, as many as 22% of patients with endomyocardial biopsy-confirmed AL cardiomyopathy had grade 2 or 3 uptake on Tc-99m PYP or DPD scans. Hence, it is critical to exclude a monoclonal process irrespective of the Tc-99m PYP scan results to confirm the diagnosis.10

What is the best matrix size to use?
The American Society of Nuclear Cardiology (ASNC) Practice Points and the Multimodality Imaging Expert Consensus recommend the following: Matrix – Planar: 256x256; Matrix – SPECT 128x128.11,32

Do you use a gamma camera or SPECT/CT?
SPECT or SPECT/CT can be used for Tc-99m PYP imaging. It is important that SPECT (when available SPECT/CT) images be acquired to differentiate blood pool activity from myocardial uptake associated with cardiac amyloidosis.

If you have female patient who fits all criteria, do you follow the same algorithm?
The same diagnostic algorithm and imaging protocol is used for both males and females.

What is the appropriate Tc-99m PYP imaging protocol to diagnose ATTR-CM?
The protocol recommended by ASNC for Tc-99m PYP imaging is described in several references.11,13,32

If a monoclonal process is excluded by serum and urine immunofixation and serum free light chain assay what statements can be made based on Tc-99m PYP images?
A grade 0 Tc-99m PYP cardiac uptake excludes ATTR cardiac amyloidosis for the most part. However, in patients with typical features of infiltration on echocardiography or CMR an endomyocardial biopsy may be considered. This is because certain forms of hereditary cardiac amyloidosis may show no uptake of bone avid tracers,33,34 Grade 2 or 3 Tc-99m PYP myocardial uptake is highly specific for ATTR-CM (provided a plasma cell dyscrasia is excluded) and may eliminate the need for endomyocardial biopsy with a positive predictive value of 98%.10,11,35
Findings on Tc-99m PYP Images

What is the H/Cl ratio?
The heart to contralateral lung ratio (H/CL) has been used to semi-quantitatively evaluate the amount of Tc-99m PYP in the myocardium. For more details readers are referred to the ASNC/Multisocietal Consensus recommendations and the ASNC Practice Points.11,32

What do you do next when Tc-99m PYP images show grade 1 uptake, and the echo has shown abnormal strain with apical sparing or if the Tc-99m PYP scan results are equivocal?
In the case of a grade 1 or equivocal Tc-99m PYP scan and an echo showing an abnormal strain pattern with apical sparing, AL amyloidosis should be excluded using serum FLC assay, serum, and urine immunofixation electrophoresis.11 In some instances an endomyocardial biopsy can be considered, as certain forms of hereditary ATTR cardiac amyloidosis may manifest as negative PYP scans.

When is peak uptake of Tc-99m PYP achieved post injection?
Based on animal studies for myocardial infarction, and one clinical study from the London group where four patients were scanned with planar imaging at multiple time points after injection of DPD, peak myocardial Tc-99m PYP/DPD uptake is likely one hour post injection of radiotracer.36 However, imaging at 2 to 3 hours is recommended to allow for clearance of tracer from the blood pool.

What is the sensitivity or negative predictive value (NPV) of Tc-99m PYP?
In a large study by Gillmore and colleagues, the sensitivity of Tc-99m PYP imaging using visual grade 2 or 3 myocardial activity in patients with heart failure along with typical imaging features on echocardiography or MRI, and after exclusion of a clonal process was 70%.10

As more Tc-99m PYP studies are ordered to diagnose ATTR-CM at an earlier stage or in the community setting, do you anticipate more Grade 1 results or just mildly elevated H/CL ratio?
Centers are already noting more Grade 1 patterns, focal patterns and more equivocal H/CL ratios are emerging. More studies are warranted to understand these patterns. It is important to rule out AL and to make sure blood pool activity does not confound the interpretation.11,32

What can cause false-positive Tc-99m PYP studies?
Causes of false positive studies include hydroxychloroquine cardiotoxicity, myocardial infarction (typically regional and not diffuse), focal rib uptake (on planar images), and other rare forms of cardiac amyloidosis.11,13,35 Gillmore reported approximately 30% of patients with AL amyloidosis have positive Tc-99m PYP studies. Exclusion of AL amyloidosis is essential.10

Are there false-negative ATTR Tc-99m PYP studies?
Several studies have reported false negative Tc-99m PYP studies in patients with certain TTR mutations including Phe64Leu.33,37

Why does a large infarct area not show Tc-99m PYP uptake as it happens with Tc-99m MDP imaging due to calcification?
Tc-99m PYP uptake may be seen in patients with myocardial infarction particularly in the first 6 weeks. Typically, uptake is regional and not diffuse as with cardiac amyloidosis. This is a limitation of this method and infarction must be excluded when interpreting of images with focal uptake.11,35 In regions with dense myocardial scar, typically months to years after infarction, no PYP Tc-99m uptake may be seen.

Blood Pool Activity on Tc-99m PYP Images

What is the optimum delay time to avoid blood pool?
The optimal delay time to minimize blood pool activity is 2 to 3 hours after injection of radiotracer as recommended in the recent addendum to the Multisocietal Imaging Expert Consensus Recommendations.11
In which patients can substantial blood pool be seen on Tc-99m PYP scans?
- Renal dysfunction
- Very elderly patients with normal LVEF without renal dysfunction
- Early imaging post injection

What should be done with patients who have blood pool activity at 1 hour?
Patients who have blood pool activity at 1 hour should be imaged using SPECT or SPECT/CT with repeat imaging at 2 to 3 hours.11

If you image beyond 1 hour, do you adjust the H/CL ratio down to 1.3 or another value?
For imaging at 3 hours the H/CL ratio threshold of 1.3 is useful.38

For throughput, we prefer to have patients with normal EF imaged 1 hour after injection. Do you feel patients need 3-hour images? If not, can we still comment on the qualitative report or only on the quantitative?
If persistent blood pool activity is noted on the 1-hour images on SPECT, imaging is repeated at 2 to 3 hours.11

What should be done with Grade 1 uptake at centers that cannot do myocardial biopsy? Should the Tc-99m PYP scan be repeated?
There are no clear recommendations on repeating a Tc-99m PYP scan. AL amyloidosis needs to be excluded. A cardiac MRI is another option.11

What are the criteria for 3-hour SPECT imaging?
The 3-hour SPECT images, if visually positive (uptake in the myocardium equal to or greater than rib uptake), can be considered positive. There is no data on diagnostic criteria for SPECT quantitation. A planar HCL ratio of >1.3 at 3 hours can be considered positive if SPECT shows myocardial uptake.11

Will residual Tc-99m PYP blood pool activity always resolves by 3 hours? What do you do with persistent blood-pooling at 3 hours?
Residual blood pool Tc-99m PYP uptake can persist for 2 to 3 hours or even longer in some patients. We recommend review of SPECT/CT imaging in those cases.

How often do you see clearing of SPECT blood pool at 3 hours when present on 1-hour images?
No published data is available. Clinical experience indicates, in most cases, the blood pool activity resolves within 3 hours.

Can adequate hydration reduce blood pool activity by 1 hour imaging?
We are not aware of any data to suggest that hydration can reduce blood pool activity.

Is the sensitivity and specificity the same when imaging at 1 hour and 3 hours?
Diagnostic accuracy for Tc-99m PYP imaging is similar for 1-hour compared to 3-hour imaging.39,40 The 1-hour images are slightly more sensitive and less specific, while the 3-hour images are less sensitive and more specific, but with similar overall accuracy.38 In order to achieve a high level of diagnostic accuracy with 1-hour imaging, ideally, physicians must develop expertise to interpret blood pool activity in a large number of cases where both time-point imaging and SPECT are performed. For all sites that are starting new cardiac amyloidosis imaging programs, imaging at 2 to 3 hours post imaging is recommended.

Are there protocols that utilize cardiac-designated cameras like Spectrum Dynamics or GE D530?
There are several publications describing the use of cadmium-zinc-telluride (CZT) cameras for the diagnosis to ATTR-CM.41-43 Cardio centric scanners that focus image acquisition on the myocardium and rib uptake may be less discernable. Visual grading of myocardial activity in relation to rib activity may be challenging to interpret.
Other Tracers for Imaging Cardiac Amyloidosis

What about PET amyloid tracers in cardiac amyloidosis?
F-18 florbetapir, F-18 florbetaben, and F-18 flutemetamol are approved to detect beta-amyloid aggregates in the brain. Researchers are investigating the use of these tracers to image cardiac AL and ATTR amyloidosis with several small single-center publications.

Therapy for Cardiac Amyloidosis

Which drugs are FDA approved for targeted treatment of ATTRv or ATTRwt-related cardiomyopathy?
Tafamidis (Vyndamax®) is currently the only FDA drug approved to treat ATTRv or ATTRwt. Inotersen (Tegsedi™) and patisiran (Onpattro™) are approved treatments of peripheral nerve disease caused by ATTRv in adult patients.

What are the mechanisms for ATTR silencers and stabilizers?
Transthyretin tetramer stabilizers are small molecules that influence the rate-limiting step in the formation of amyloid fibrils and the dissociation of TTR tetramers into amyloidogenic monomers. By binding to the thyroxin binding site on TTR with high affinity and selectivity, in vitro studies showed tafamidis induces dose-dependent kinetic stabilization of ATTRwt and a range of ATTRv variants (i.e., V30M, V122I, etc.).

Antisense oligonucleotides (ASO) can employ two distinct regulatory mechanisms, depending on their molecular design. These are steric blocking, in which ASOs prevent translation by plain occupancy of the mRNA, and enzymatic mechanisms inducing RNA cleavage or degradation. Silencer medications act on the liver to decrease the production of TTR. Two ATTR silencers are approved by the FDA to treat patients with ATTRv who also have neuropathy, patisiran and inotersen.

Are there any side effects associated with tafamidis?
No major side effects were noted in the phase 3 clinical trial of tafamidis. Prior to prescribing, it is important to consult the full prescribing information.

When is diflunisal used?
Diflunisal is a non-steroidal anti-inflammatory drug that stabilizes TTR, with limited data available regarding effects on cardiac structure and function. In a study of 81 patients with ATTR-CM, Lohrmann and coworkers showed diflunisal treatment resulted in measurable differences in some parameters of cardiac structure and function after only 1 year of administration. Differences in TTR concentration and favorable differences in left atrial volume index and cardiac troponin 1 were measured. Among the subset with ATTRwt, diflunisal treatment was associated with differences in global longitudinal strain. Changes in wall thickness, left ventricular ejection fraction, and BNP were similar between the treated and untreated groups. Although used clinically in some patients, this is not FDA approved therapy for ATTR cardiac amyloidosis.

Which class of drugs is most used to treat heart failure in cardiac ATTR amyloidosis?
Loop diuretics are used for decongestion, although they may compromise renal function or systemic perfusion in patients with advanced restrictive disease because diminishing preload may compromise an already fixed stroke volume, leading to low cardiac output.

Readers are recommended to reference key publications outlining the details of heart failure therapy in cardiac amyloidosis.
General Reviews and Recommendations for Cardiac Amyloidosis


References

31. Hutt D, Quigley AM, Page J, et al. Utility and limitations of 3,3-diphosphono-1,2-propanodicarboxylic acid


ASNC thanks Sharmila Dorbala, MD, MPH, MASNC for her contributions to this document.