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# Advances in the Diagnosis and Management of Transthyretin Amyloid Cardiomyopathy

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## Abstract

*Purpose of review* Transthyretin amyloid cardiomyopathy (ATTR-CM) is a disease with high morbidity and mortality. This disease is significantly underdiagnosed and is more common than previously appreciated, particularly among older adults and people of African descent. This review discusses recent advances in the diagnosis and treatment for ATTR-CM.
*Recent findings* Historically, ATTR-CM was diagnosed via endomyocardial biopsy, a resource-intensive and invasive approach. However, in most cases, ATTR-CM can now be diagnosed non-invasively using bone tracer cardiac scintigraphy, which may facilitate earlier diagnosis. In recent clinical trials, a transthyretin stabilizer (tafamidis) and transthyretin gene silencers (patisiran and inotersen) have emerged as effective ATTR amyloidosis therapies and have been approved for use in the USA and many other countries.
*Summary* ATTR-CM is now recognized as an important cause of heart failure. Approaches to the diagnosis and treatment of ATTR-CM are rapidly evolving. Now, more than ever, there are opportunities to improve clinical care of patients with this challenging disease.

## Introduction

Transthyretin (TTR) is a 127-amino acid protein synthesized and secreted by the liver. This protein serves primarily as a transporter of thyroxine and retinol binding protein. In transthyretin amyloidosis (ATTR), the native homotetramer form dissociates into unstable TTR monomers, which misfold, aggregate, and ultimately form rigid amyloid fibrils. These fibrils deposit in a variety of tissues and can lead to ATTR cardiomyopathy (ATTR-CM) and ATTR neuropathy. ATTR-CM is associated with a progressive restrictive cardiomyopathy, heart failure, arrhythmias, and sudden death. ATTR-CM can result either from amyloid deposits comprised of wild-type TTR (ATTRwt) or variant TTR (ATTRv) caused by a TTR gene mutation [1–4]. ATTRwt is predominantly a disease of older men and is associated with cardiac, tendon, and ligament involvement. ATTRv is an autosomal dominant disease with incomplete penetrance and can have a more variable pattern of organ involvement depending on the specific TTR mutation. Cardiomyopathy and/or neuropathy is the most common ATTRv manifestation.

Previously thought to be a rare disorder, ATTR-CM is now considered an important cause of heart failure with preserved ejection fraction (HFPEF), particularly among older adults and Blacks [5]. In a post-mortem study, ATTRwt cardiac amyloidosis was observed in approximately one in four people over 85 years old at the time of death [6]. A study of patients over 60 years old with heart failure with preserved ejection fraction and left ventricular (LV) wall thickness > 12 mm found that 13% had a positive bone tracer cardiac scintigraphy study consistent with ATTR-CM [7]. In a study of patients 75 years or older without suspected ATTR-CM who underwent a bone scan, almost 3% showed myocardial uptake concerning for amyloid deposition [8]. Finally, specific racial and ethnic groups may have a higher risk for developing ATTR-CM. For instance, in the USA, 3–4% of Blacks carry the amyloidogenic Val122Ile TTR variant, which has been associated with an increased risk of heart failure [9, 10].

ATTR-CM is a progressive, incurable disease with high morbidity and mortality. Therefore, early diagnosis is crucial to initiate one of the emerging ATTR-specific therapies to halt further amyloid deposition and avoid further end-organ damage [11]. Often, extracardiac manifestations of ATTR amyloidosis are present years before significant cardiac dysfunction is apparent. A history of carpal tunnel syndrome [1, 12–14], biceps tendon rupture [15], lumbar spinal stenosis [16, 17], or symptoms of polyneuropathy or dysautonomia in a patient with heart failure should raise suspicion for ATTR amyloidosis [11]. Laboratory studies may show chronic mildly elevated troponin levels in the absence of myocardial ischemia [1, 7, 11]. An electrocardiogram (ECG) may reveal a mismatch between QRS voltage amplitude and LV wall thickness, conduction disease, or a pseudo-infarct pattern—though many patients with ATTR cardiomyopathy will have normal electrical voltages [11]. The presence of any of these clinical findings should prompt further cardiac testing to screen for cardiac amyloidosis (summarized in Table 1).

# Diagnosis

## Screening tests: echocardiogram and cardiac magnetic resonance

Echocardiography and/or cardiac magnetic resonance imaging (CMR) is a common initial study in the evaluation for ATTR-CM. Current guidelines recommend pursuing confirmatory testing for cardiac amyloidosis when there is clinical suspicion *and* suggestive echocardiographic or CMR findings [18, 19].

### Echocardiography

Abnormal echocardiographic findings often initiate the diagnostic cascade for ATTR-CM. However, echocardiography is neither sensitive nor specific for the diagnosis of ATTR-CM. Patients may have a normal or near-normal appearing echocardiogram early in the disease course [20]. A common finding is

**Table 1. Key characteristics of diagnostic modalities for ATTR-CM**

| Diagnostic modality | Accessibility | Clinical scenario | Suspicious or diagnostic criteria | Diagnostic test properties | Limitations |
|---|---|---|---|---|---|
| Echocardiography | Widely accessible | Screening | -Biventricular increased wall thickness<br>-Diastolic dysfunction<br>-Abnormal longitudinal strain with apical sparing | N/A | Non-specific for ATTR-CM |
| Cardiac magnetic resonance | Increasingly accessible but costly | Screening | -Biventricular increased wall thickness<br>-Diffuse LGE<br>-Inability to null the myocardium<br>-Increased ECV (> 0.40) | N/A | Non-specific for ATTR-CM |
| Endomyocardial biopsy | Technical expertise often limited to larger medical centers | Gold standard for diagnosis | -Apple green birefringence on Congo red staining<br>-Amyloid subtype determined by immunohistochemistry and/or mass spectrometry | -Nearly 100% sensitivity and specificity<br>-Note fat pad biopsy has a sensitivity of only 15–45% | Small risk of procedural complications (bleeding, cardiac tamponade, valvular damage) |
| Bone tracer cardiac scintigraphy | Widely accessible | Can be used for diagnosis once monoclonal protein has been ruled out | -H/CL ratio > 1.5<br>-Cardiac uptake greater than or equal to bone uptake | Approaches 100% sensitivity when combined with a negative workup for monoclonal protein (SPIE, UPIE, serum FLC ratio) | -Does not characterize cardiac anatomy<br>-Cannot be used if a monoclonal protein is present<br>-Can have false positives from blood pool uptake if SPECT is not performed<br>-Can have false negatives with some rare mutations |

*ATTR* transthyretin amyloidosis, *CM* cardiomyopathy, *ECV* extracellular volume, *FLC* free light chain, *H/CL* heart to contralateral, *LGE* late gadolinium enhancement, *N/A* not applicable, *SPECT* single-photon emission computed tomography, *SPIE* serum protein electrophoresis with immunofixation, *UPIE* urine protein electrophoresis with immunofixation

biventricular "hypertrophy" (not true muscle hypertrophy, but rather increased wall thickness) with concentric LV wall thickness > 12 mm [21, 22]. Up to half of patients may have a small pericardial effusion [7, 21, 23]. Tissue Doppler may demonstrate diastolic dysfunction. In both ATTR-CM and light chain amyloid cardiomyopathy (AL-CM), LV longitudinal strain is often reduced with apical strain being relatively preserved compared with wall segments [21]. This pattern of apical sparing can be helpful for suggesting a diagnosis of cardiac amyloidosis rather than other causes of increased LV wall thickness, such as hypertrophic cardiomyopathy and hypertension [24].

### Cardiac magnetic resonance

CMR offers excellent characterization of the myocardium and can be helpful for evaluating various forms of cardiomyopathy. For cardiac amyloidosis, CMR can provide some information about the location and extent of cardiac amyloid deposition. Common CMR findings seen in cardiac amyloidosis include biventricular hypertrophy, diffuse late gadolinium enhancement (LGE), and markedly increased extracellular volume fraction (ECV) [25]. Interatrial septum and atrioventricular valve thickening may also be seen [11, 19]. In cardiac amyloidosis, abnormal blood pool nulling and gadolinium kinetics have been associated with increased mortality [26–29]. LGE has inconsistently been associated with mortality in amyloid-CM. ECV is used to quantify the interstitial volume in the myocardium [19]. In amyloid cardiomyopathy, and other infiltrative diseases, the interstitial space is expanded due to amyloid, fibrosis, and other substances. In cardiac amyloidosis, ECV is significantly increased compared with healthy subjects and is associated with increased mortality [25, 30]. Importantly, while the abovementioned CMR findings can highly suggestive of cardiac amyloidosis, further confirmatory testing is required to distinguish among ATTR-CM, AL-CM, or other forms of cardiac amyloidosis. Therefore, once there is clinical suspicion for cardiac amyloidosis based on echocardiography and other clinical characteristics, CMR does not save any steps in confirming a diagnosis and can often be skipped—its main role may be in raising suspicion for amyloidosis when it did not previously exist.

## Confirmatory tests: endomyocardial biopsy and bone tracer cardiac scintigraphy

### Endomyocardial biopsy

Endomyocardial biopsy is the gold standard for diagnosing ATTR-CM, with a near 100% sensitivity and specificity for ATTR-CM; in contrast, the sensitivity for abdominal fat pad biopsy is considerably lower (15–45%) [31]. Amyloid deposition can be readily detected by histology. Congo red staining of amyloid fibrils, regardless of the precursor protein, show apple green birefringence under polarized light. The amyloid fibril subtype (e.g., ATTR, AL, or other) can be determined by immunohistochemistry staining, which is routinely available in clinical laboratories. However, this method has somewhat limited diagnostic accuracy, particularly in less-experienced hands [32, 33]. Therefore, laser capture microdissection with mass spectrometry, which has a sensitivity and specificity up to 98% and 100%, respectively, should be considered for definitive amyloid subtyping [33, 34]. Endomyocardial biopsies are generally safe and have a high

diagnostic yield. However, they may be expensive due to the costs of the procedure and pathologic interpretation, and they require technical expertise which may not be available at many medical centers [20].

## Bone tracer cardiac scintigraphy

Bone tracer cardiac scintigraphy has emerged as an accurate, non-invasive test alternative to endomyocardial biopsy. The mechanism by which these bone tracers bind avidly to ATTR amyloid deposits is unclear but may be due to microcalcifications within the amyloid deposits. Cardiac scintigraphy can be performed with $^{99m}$Tc-pyrophosphate ($^{99m}$Tc-PYP), $^{99m}$Tc-3,3 diphosphono-1,2propanodicarboxylic acid ($^{99m}$Tc-DPD), or $^{99m}$Tc-hydroxymethyline diphosphonate ($^{99m}$Tc-HMDP); only $^{99m}$Tc-PYP is available in the USA. The bone radiotracer is injected, and planar and/or single-photon emission computed tomography (SPECT) images are obtained 1–3 h later, depending on the protocol. A quantitative score is calculated by comparing the amount of tracer uptake in the heart compared with the contralateral lung space (H/CL ratio) [18, 27]. The cutoff value for a positive depends on the time point used for image acquisition. Qualitative assessment consists of measuring the degree of heart uptake compared with sternal update. Grade 0 refers to no cardiac uptake. Grade 1 refers to cardiac uptake less than the ribs. Grade 2 is cardiac uptake equal to ribs, and grade 3 is cardiac uptake greater than the ribs. Grade 2–3 is considered to be a positive study.

If used appropriately, cardiac scintigraphy has a sensitivity approaching 100% for diagnosing ATTR cardiomyopathy [35, 36••, 37•, 38]. However, several important caveats warrant further discussion. First, AL-CM also can result in increased cardiac scintigraphy uptake (~ 22% of cases) [36••]. AL-CM can be rapidly fatal and requires prompt treatment with chemotherapy/immunotherapy. Thus, a delayed or missed diagnosis of AL-CM due to inappropriate bone scintigraphy testing can have devastating consequences. The current societal guidelines require that cardiac scintigraphy only be used to diagnose ATTR-CM if the presence of a monoclonal gammopathy has been ruled. AL amyloidosis results from a monoclonal plasma cell or B cell proliferation that produces an amyloidogenic free light chain. Negative serum and urine immunoelectrophoresis combined with a normal serum free light chain ratio have a 99% negative predictive value for AL amyloidosis [18, 27, 39]. For suspected ATTR-CM patients with an abnormal hematologic assessment, a biopsy is required, with no role for bone tracer cardiac scintigraphy [18].

Another point to consider is that the diagnostic characteristics for cardiac scintigraphy were mostly determined from studies performed at specialized referral centers with ATTR-CM already confirmed by endomyocardial biopsy. Therefore, the diagnostic accuracy of this test may be different in a real-world setting, particularly among patients with very early-stage ATTR-CM [18]. Furthermore, the diagnostic accuracy may vary based on the ATTR subtype. For instance, a recent study found a substantially lower sensitivity (11%) for patients with the Phe64Leu TTR variant [40•]. This finding may be partially influenced by the study design, reference standard used (only 3/26 patients underwent endomyocardial biopsy), and the time period when the study was conducted which

spanned 25 years, during which the clinical diagnosis and management of ATTR-CM has likely evolved [41]. Nevertheless, more studies are needed for cardiac scintigraphy in patients with less common TTR variants.

Finally, false positives may occur in certain situations. Planar imaging may appear positive based on radiotracer uptake in the blood pool or overlying bones and soft tissues [18]. Thus, it is important to also obtain SPECT images to avoid this artifact. In addition to AL amyloidosis, other conditions that can lead to a false positive study include rare causes of cardiac amyloidosis, such as apolipoprotein A-I amyloidosis [36••], and hydroxychloroquine-related cardiomyopathy [42].

Despite these limitations, cardiac scintigraphy is a sensitive test that is able to detect ATTR-CM, sometimes even before echocardiographic changes are evident [43]. As a non-invasive and widely available test, cardiac scintigraphy is increasingly the most common way patients with ATTR amyloid cardiomyopathy are diagnosed, and will likely play an essential role in developing systematic screening protocols for high-risk groups to promote early diagnosis. Questions that will need to be addressed include its diagnostic accuracy for early-stage ATTR-CM and for various ATTR variants. Moreover, what is the potential role for cardiac scintigraphy screening in asymptomatic carriers of a TTR variant? Further real-world, practice-based data are needed to optimize the use of this promising imaging modality.

## Advances in screening

Given the availability of low-burden, confirmatory testing with cardiac scintigraphy, an algorithm has been proposed for screening high-risk patients. Based on the recommendations of this algorithm, men > 65 years old and women > 70 years old, with increased LV wall thickness (≥ 14 mm) and suspicious signs or symptoms, should undergo screening with cardiac scintigraphy after AL amyloidosis has been ruled out [11].

Current consensus statements do not recommend cardiac scintigraphy for screening of asymptomatic individuals. However, abnormal cardiac scintigraphy findings may precede symptoms in patients with known ATTR mutations. Though the efficacy of treatment in this patient population has not been tested [44], several recent and ongoing studies aim to assess methods for early identification of ATTR-CM. The ongoing Screening for Cardiac Amyloidosis in Using Nuclear Imaging for Minority Populations (SCAN-MP) study will assess the utility of cardiac scintigraphy for diagnosing ATTR-CM in Hispanic Caribbean and Black patients with heart failure not caused by valvular or ischemic heart disease [45]. Other ongoing studies and recently completed studies seek to identify the prevalence of ATTR-CM in patients with HFpEF using natural language processing methods [46], and in patients undergoing surgery for idiopathic carpal tunnel syndrome [47] or trigger finger release [48].

## Advances in treatment

Historically, the treatment options for ATTR amyloidosis were limited and comprised mostly symptomatic care (e.g., diuretics to manage heart failure).

ATTRv polyneuropathy patients could undergo liver transplantation to remove the source of amyloidogenic TTR synthesis [49]. However, the risk of transplant-related complications must be considered, and organ supply is limited. Furthermore, post-transplant patients can still have progression of ATTRv neuropathy. As for ATTR-CM, in carefully selected patients, heart transplantation may be an option with outcomes similar to those transplanted for other types of cardiomyopathy [50]. However, many patients with ATTR-CM are not transplant candidates because of their age and comorbidities. Given these limitations and insufficient organ availability, there has been significant interest in developing ATTR-specific therapies that can halt or reverse the disease.

Recent clinical trials have identified 2 classes of effective therapies. TTR stabilizers bind to the TTR tetramer, preventing dissociation into amyloidogenic monomers, the rate-limiting step in amyloid formation. TTR silencers disrupt TTR mRNA, thereby reducing hepatic production of wild-type and variant TTR protein. Finally, though efficacy data is limited to date, monoclonal antibodies which may promote the clearance of amyloid deposits from organs are also being pursued (Table 2).

## Transthyretin stabilizers

### Tafamidis

Tafamidis is currently the only FDA-approved therapy for ATTR-CM. This oral medication is a small molecule that stabilizes the TTR tetramer by binding to transthyretin's thyroxine binding site [51, 52]. It was initially tested in a phase 2/3 randomized trial of 125 ATTRv polyneuropathy patients. The study power was reduced because 21% of patients underwent liver transplantation during the trial and were counted as non-responders in the pre-specified analyses. The trial showed a non-statistically significant trend toward improvement in neuropathic symptoms in the tafamidis arm. These results led to drug approval in Europe, Japan, and Latin America, but not the USA [53].

The landmark phase 3 ATTR-ACT trial led to the FDA approval of tafamidis for the treatment of ATTR amyloid cardiomyopathy. In this international double-blind, placebo-controlled trial of patients with ATTRwt (76%) and ATTRv (24%) cardiomyopathy, tafamidis was shown to be highly effective in slowing disease progression. Four hundred forty-one patients were allocated in a 2:1:2 ratio to placebo, low-dose (20 mg), or high-dose (80 mg) tafamidis [54]. At 30-month follow up, tafamidis reduced the hierarchical composite endpoint of all-cause mortality and cardiovascular-related hospitalization, and showed statistically significant improvements in both outcomes independently. Kaplan-Meier curves showed a mortality benefit as early as 18 months. Patients with NYHA class III symptoms at baseline had less benefit than patients with baseline NYHA class I–II symptoms, emphasizing the importance of early diagnosis. Tafamidis was also associated with the key secondary endpoints of a slower decline in 6-min walk distance and Kansas City Cardiomyopathy Questionnaire score. There were no notable adverse events which occurred in higher proportion in the tafamidis arm than the placebo arm [55••]. Tafamidis, a life-long medication, carries a cost of approximately $225,000

**Table 2. Recent and ongoing notable ATTR therapeutic clinical trials**

| Drug name *Trial name* | Number of patients | Route | Main findings and primary outcomes | Adverse effects | Other considerations | FDA approval indication |
|---|---|---|---|---|---|---|
| Transthyretin stabilizers | | | | | | |
| Tafamidis *ATTR-ACT* | 441 | Oral | Decreased mortality and cardiovascular-related hospitalizations. | None | Very costly | ATTRwt and ATTRv cardiomyopathy |
| AG10 *ATTRibute-CM* | 510 | Oral | *Results pending*: Primary outcomes will be change in 6-min walk test and the composite of all-cause mortality and cardiovascular hospitalizations. | *Pending* | Phase 2 trial showed improved TTR stabilization. | *Trial ongoing* |
| Transthyretin silencers | | | | | | |
| Patisiran *APOLLO* | 225 (with neuropathy ± | | cardiomyopathy) | IV | Vastly improved neurological function vs. placebo. Subanalysis showed decreased LV wall thickness, decreased NT-ProBNP, and improved global longitudinal strain. | Infusion reactions |
| Requires premedication. Vitamin A supplementation recommended. | ATTRv | | polyneuropathy or mixed | | | |

polyneuropathy/cardiomyopathy Vutrisiran *HELIOS-B*600SQ*Results pending*: Primary outcome will be the composite of all-cause mortality and cardiovascular-related hospitalizations.*Pending**Pending**Trial ongoing* Inotersen *Neuro-TTR*172 (with neuropathy ± cardiomyopathy)SQGreatly improved neurological function vs. placebo. No significant difference in cardiac parameters.Thrombocytopenia, glomerulonephritisSerial monitoring of platelet count and renal function recommended.ATTRv polyneuropathy or mixed polyneuropathy/cardiomyopathy AKCEA-TTR-LRx *CARDIO*-TTRansform750SQ*Results pending:* The primary outcome will be the change in 6-min walk test and the composite of cardiovascular mortality and clinical cardiovascular events.*Pending**Pending**Trial ongoing*Amyloid clearance PRX00436IVMaximum tolerated dose and treatment-emergent adverse events*Pending*Phase I trial*Trial ongoing**ATTR* transthyretin amyloidosis, *ATTRv* variant ATTR, *ATTRwt* wild-type ATTR, *IV* intravenous, *SQ* subcutaneous, *TTR* transthyretin

dollars per year, a substantial burden to both individual patients and healthcare systems [56]. Its cost-effectiveness continues to be debated [57].

### AG10

AG10 is another oral TTR stabilizer that binds to form hydrogen bonds with TTR similar to those present in T119M mutation (a mutation associated with increased life expectancy and thought to be protective by super-stabilizing TTR tetramers). A phase 2 trial enrolled 49 subjects with ATTR-CM and NYHA stage II or III heart failure who were randomized to either placebo, or AG10 400 mg twice daily or AG 800 mg twice daily. Outcome measures included changes in serum TTR concentration, given that higher levels of TTR are independently associated with improved survival in ATTR-CM [58]. Subjects in the placebo arm had a decrease in serum TTR, while subjects in both AG10 arms had a statistically significant increase in serum TTR from baseline. Both active doses resulted in greater than 90% ATTR stabilization at day 28. The frequency of adverse events did not significantly differ among the 3 groups [59]. An ongoing, phase 3 randomized trial, ATTRibute-CM, aims to enroll 510 patients with symptomatic ATTR-CM randomized to receive twice daily 800 mg AG10 versus placebo with a primary outcome of change in 6-min walk distance at 12 months and a composite outcome of all-cause mortality and cardiovascular-related hospitalizations at 30 months. Notably, subjects cannot enroll if they are taking tafamidis, potentially impacting enrollment in countries where tafamidis is approved and considered the standard-of-care [60].

### Diflunisal

Several other compounds have transthyretin-stabilizing properties. Diflunisal, a non-steroidal anti-inflammatory drug (NSAID), also binds to the thyroxine binding site of transthyretin, and was tested in a randomized trial for patients with ATTR polyneuropathy. In this study, subjects randomized to diflunisal had significantly slower neurological deterioration compared with those randomized to placebo [61]. Diflunisal was associated with decreased mortality and rate of heart transplantation in one observational study [62]. In a single-center, retrospective cohort of 23 patients with ATTR-CM, diflunisal was not associated with higher frequency of adverse events [63]. However, the emergence of tafamidis and AG10 as well as concerns about the long-term risks of NSAIDs in patients with cardiac and renal dysfunction likely limit diflunisal's widespread use.

## Transthyretin silencers

### Patisiran

Patisiran is an anti-TTR RNA interference molecule that reduces hepatic TTR production. A phase 2 study in ATTRv polyneuropathy showed > 80% TTR knockdown in patients who received patisiran. Patisiran is administered every 3 weeks via intravenous infusion. Approximately 10% of participants experienced infusion reactions [64]. The drug requires premedication with dexamethasone, acetaminophen, and antihistamines. Given the potential risk of

impaired vitamin A transport with TTR lowering, vitamin A supplementation is also recommended [64].

The phase 3, multinational, randomized, placebo-controlled APOLLO trial tested the efficacy of patisiran in 225 patients with ATTRv polyneuropathy [65]. Patients with prior liver transplantation or undergoing evaluation for liver transplantation were excluded, as were patients with severe heart failure (NYHA class > 2), uncontrolled cardiac arrhythmias, or unstable angina. At 18 months, the patisiran group actually demonstrated a small improvement in neurological function as evidenced by the modified Neuropathy Impairment Score + 7. In contrast, the placebo group had dramatically progressive neurologic impairment, consistent with the natural history of the disease [66••].

An exploratory analysis of 126 APOLLO patients with cardiac involvement, defined as left ventricular wall thickness > 13 mm without history of hypertension or aortic valve disease, was also performed [65, 66••]. Mean LV wall thickness was reduced in the patisiran group compared with placebo. A significantly higher proportion of patisiran patients had an improvement of > 2% in global longitudinal strain compared with placebo (21.3% versus 8%) and more specifically, basal strain [67, 68•]. Patients who received patisiran also had a 55% reduction in NT-ProBNP levels compared with placebo [67, 68•]. Based on the APOLLO trial, patisiran is FDA-approved for patients with ATTRv polyneuropathy or mixed polyneuropathy/cardiomyopathy.

Vutrisiran, a next generation RNA interference therapy that is administered subcutaneously every 3 months, is currently being tested in a randomized trial of 600 patients with ATTR-CM. A subset of the trial participants will be allowed to take commercially available tafamidis. The primary outcome will be a composite of all-cause mortality and cardiovascular-related hospitalizations [70, 71].

### Inotersen

Inotersen is an antisense oligonucleotide that degrades TTR messenger RNA, leading to reduced TTR synthesis. Inotersen is administered weekly as a subcutaneous injection. Inotersen was studied in the phase 3 NEURO-TTR trial, which enrolled 172 patients with ATTRv polyneuropathy. At 66 weeks, the decline in neurologic function was significantly less in the inotersen group compared with placebo, though the difference was not as dramatic as with patisiran in the APOLLO trial. Severe adverse events in the inotersen group included thrombocytopenia (3%) and glomerulonephritis (3%). In cardiac sub-analyses, there was no significant difference in LV wall thickness or global longitudinal strain between the 2 groups [72••]. Based on the NEURO-TTR trial, inotersen is FDA-approved for patients with ATTRv polyneuropathy or mixed polyneuropathy/cardiomyopathy.

AKCEA-TTR-LX is a more potent, next generation antisense oligonucleotide. The phase 3 trial placebo-controlled randomized trial is now enrolling 750 patients with ATTR-CM; patients will be allowed to receive commercial tafamidis. The primary outcome will be the composite of cardiovascular mortality and cardiovascular events [73, 74].

## Amyloid clearance

PRX004 is a humanized IgG1 monoclonal antibody designed to target misfolded ATTR via a cryptic epitope and promote clearance of amyloid

deposits. A multinational phase I trial of 32 subjects with ATTR cardiomyopathy and/or neuropathy is ongoing (NCT03336580) [52, 75, 76].

## Conclusion

ATTR-CM is a morbid and life-threatening disease that is increasingly recognized as an important cause of heart failure, particularly in older adults and black patients. The standard practice for the diagnosis of ATTR-CM in most patients is transitioning from endomyocardial biopsy to bone tracer cardiac scintigraphy. Several ongoing studies are examining the utility of large-scale screening in patient populations who are at increased risk of ATTR-CM. As cardiac scintigraphy becomes more widely used, diagnostic nuances are being uncovered. The approved medications for ATTR amyloidosis, transthyretin stabilizers and silencers, are able to halt or slow disease progression. The effects of novel therapeutics currently under investigation remain to be seen. As more patients are diagnosed, perhaps earlier in the course of disease, data will arise on the real-world effects and challenges, particularly the cost, of currently available treatment options.

Taken together, the rapidly emerging advances for the diagnosis and treatment of ATTR-CM serve to increase early detection, refine diagnostic practices, and improve outcomes for patients with this challenging and life-threatening disease.

## Compliance with Ethical Standards

**Conflict of Interest**

Dr. Spencer-Bonilla does not have any conflict of interest to disclose. Dr. Alexander has received an investigator-initiated research grant from Pfizer and has received consulting fees (modest) from Alnylam, Eidos, and Pfizer. Dr. Witteles has received consulting fees (modest) from Pfizer, Eidos, and Alnylam.

**Human and Animal Rights**

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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## Publisher's Note