Circulation

AHA SCIENTIFIC STATEMENT

Cardiac Amyloidosis: Evolving Diagnosis and Management

A Scientific Statement From the American Heart Association

ABSTRACT: Transthyretin amyloid cardiomyopathy (ATTR-CM) results in a restrictive cardiomyopathy caused by extracellular deposition of transthyretin, normally involved in the transportation of the hormone thyroxine and retinol-binding protein, in the myocardium. Enthusiasm about ATTR-CM has grown as a result of 3 simultaneous areas of advancement: Imaging techniques allow accurate noninvasive diagnosis of ATTR-CM without the need for confirmatory endomyocardial biopsies; observational studies indicate that the diagnosis of ATTR-CM may be underrecognized in a significant proportion of patients with heart failure; and on the basis of elucidation of the mechanisms of amyloid formation, therapies are now approved for treatment of ATTR-CM. Because therapy for ATTR-CM may be most effective when administered before significant cardiac dysfunction, early identification of affected individuals with readily available noninvasive tests is essential. This scientific statement is intended to guide clinical practice and to facilitate management conformity by covering current diagnostic and treatment strategies, as well as unmet needs and areas of active investigation in ATTR-CM.

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Cardiac amyloidosis results in 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. More than 30 proteins can form amyloid fibrils in vivo, and the classification is based on the precursor protein. Cardiac amyloidosis is caused mainly by misfolded monoclonal immunoglobulin light chains (ALs) from an abnormal clonal proliferation of plasma cells or transthyretin (TTR) amyloidosis (ATTR), a liver-synthesized protein previously called prealbumin that is normally involved in the transportation of the hormone thyroxine and retinol-binding protein. Given the paramount relevance of transthyretin amyloid cardiomyopathy (ATTR-CM) to the practicing cardiologist, this statement focuses on its diagnosis and management.

ATTR can be inherited as an autosomal dominant trait caused by pathogenic variants in the transthyretin gene *TTR* (ATTRv) or by the deposition of ATTRwt (wild-type transthyretin protein), previously called senile cardiac amyloidosis. The ATTR amyloid protein can infiltrate other organs, most often the autonomic and peripheral nervous systems, but cardiac involvement, when present, is the principal determinant of survival. Median survival after diagnosis in untreated patients is poor: 2.5 years for ATTRv caused by the *TTR* Val122Ile (or pV142I) mutation and 3.6 years for ATTRwt.[1–3]

Key Words: AHA Scientific Statements ■ amyloidosis ■ heart failure ■ transthyretin

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Over the past few years, enthusiasm about ATTR-CM has grown as a result of 3 simultaneous areas of advancement. First, imaging techniques allow accurate noninvasive diagnosis of ATTR-CM without the need for confirmatory endomyocardial biopsies. Second, observational studies indicate that ATTR-CM may be underrecognized in a significant proportion of patients with heart failure. Third, on the basis of the understanding of the mechanisms of amyloid formation, therapies are approved for treatment of ATTR-CM.

Because therapy for ATTR-CM is most effective when administered before significant symptoms (New York Heart Association [NYHA] class III–IV) of cardiac dysfunction manifest, early identification of affected individuals with readily available noninvasive tests is essential. This scientific statement is intended to guide clinical practice and management by covering current diagnostic and treatment strategies, as well as unmet needs and areas of investigation in ATTR-CM.

DIAGNOSIS

Facilitating Recognition of ATTR-CM

ATTR-CM has historically been considered rare, but the true prevalence is challenging to estimate because it is frequently underrecognized. There are many potential explanations, including the false perception that the diagnosis of ATTR-CM can be made only at expert centers through endomyocardial biopsy; the attribution of the presenting signs and symptoms to aging, hypertension, hypertrophic cardiomyopathy, and heart failure with preserved ejection fraction (HFpEF); and, until recently, the lack of disease-modifying treatments, which rendered accurate diagnosis less relevant.

ATTR-CM can be prevalent in certain clinical contexts: ATTR deposition is seen in up to 16% of patients with degenerative aortic stenosis[4] and 13% to 17% of patients with HFpEF.[5,6] Because ATTR-CM is a multisystemic infiltrative disease associated with noncardiac soft tissue deposition, patients often have carpal tunnel syndrome,[7] lumbar spinal stenosis,[8] biceps tendon rupture,[9] and autonomic or sensory polyneuropathy.

Clinical Clues to the Diagnosis of Cardiac Amyloidosis

Patients with ATTR-CM commonly present with dyspnea, fatigue, and edema, but these findings are nonspecific and often misdiagnosed as nonamyloid HFpEF, a missed opportunity. Assessment of myocardial wall thickness on echocardiogram is helpful; the presence of moderate to severe left ventricular (LV) thickening (wall thickness ≥14 mm) should trigger consideration of ATTR-CM especially if there is discordance between wall thickness on echocardiogram and QRS voltage on ECG.[10] Patients with HFpEF and a moderate to severe increase in wall thickness are often mislabeled as having hypertensive cardiomyopathy when this should prompt a broader differential, including cardiac amyloidosis, hypertrophic cardiomyopathy, aortic stenosis, and rarer genetic disorders such as Fabry disease.[11]

Table 1. Clinical Clues From Routine Cardiac Evaluation That Should Prompt Additional Diagnostic Evaluation for ATTR-CM

Traditional Cardiac Clues	Noncardiac Clues
Intolerance to antihypertensive or heart failure medications because of symptomatic hypotension or orthostasis	Neurological: sensorimotor polyneuropathy (paresthesias and weakness), autonomic dysfunction (orthostatic hypotension, postprandial diarrhea alternating with constipation, gastroparesis, urinary retention, and incontinence)
Persistent low-level elevation in serum troponin	Orthopedic: carpal tunnel syndrome, lumbar spinal stenosis, unprovoked biceps tendon rupture, hip and knee arthroplasty
Discordance between QRS voltage on an ECG and wall thickness on imaging	Black race
Unexplained atrioventricular block or prior pacemaker implantation	Family history of polyneuropathy
Unexplained LV wall thickening, right ventricular thickening, or atrial wall thickening	
Family history of cardiomyopathy	

ATTR-CM indicates transthyretin amyloid cardiomyopathy; and LV, left ventricular.

Given the nonspecific presenting findings, the key to diagnosis is a high index of suspicion. Older patients presenting with HFpEF and even milder degrees of increased wall thickness also warrant scrutiny; clinical clues are outlined in Table 1.[10,12] Family history is of particular importance because an inherited form of ATTRv, the Val122Ile mutation, is observed almost exclusively in black patients and is associated with a greater burden of autonomic and peripheral neuropathy and worse outcomes than ATTRwt.[3,11]

Last, it is important to note that <40% of patients with biopsy-proven ATTR-CM have low voltage on ECG, and these patients often have advanced disease.[13] Thus, although helpful if present, the absence of low voltage on ECG should not dissuade clinicians from considering ATTR-CM as a potential cause of HFpEF in the appropriate clinical context.

Rational Approach to Testing in Cardiac Amyloidosis

Although echocardiography offers clues that prompt further testing and cardiac magnetic resonance (CMR) imaging[14,15] may indicate an infiltrative process, the use of ^{99m}technetium (^{99m}Tc) bone-avid compounds represents a paradigm shift because these scans allow the

Table 2. Comparison of Diagnostic Imaging Modalities in ATTR-CM

	Cost	Specialized Expertise Required for Interpretation	Exposure to Ionizing Radiation	Cardiac Devices Affect Image Quality	Can Identify Nonamyloid Causes of LV Thickening	Clinical Clues Suggesting Cardiac Amyloidosis	Distinguish AL-CM and ATTR-CM	Markers of Worse Prognosis
Echocardiography	$	No	No	No	Yes (valvular disease, HCM, aortic stenosis, Fabry disease), although amyloid cardiomyopathy may also be present	Not diagnostic of cardiac amyloidosis Clinical clues suggestive of an infiltrative cardiomyopathy: pericardial or pleural effusions, thick right ventricle, small LV cavity, and impaired global longitudinal strain characteristically with sparing of the apex	No	Lower EF, greater regional variation in global longitudinal strain, worse global longitudinal strain, lower stroke volume[19]
MRI	$$	Yes	No	Yes	Yes (infiltrative disease, HCM)	Not diagnostic of cardiac amyloidosis Clinical clues suggestive of cardiac amyloidosis: elevated native T1, increased extracellular volume fraction, late gadolinium enhancement pattern (diffuse, subendocardial, or transmural), abnormal gadolinium kinetics	No	Late gadolinium enhancement, higher extracellular volume fraction[20]
Bone scintigraphy	$	No	Yes	No	No	Diagnostic for ATTR-CM if normal light chain assays and grade 2/3 cardiac uptake or an H/CL ratio of >1.5 False positives may occur from AL-CM amyloidosis (why assessment for monoclonal proteins is essential), previous myocardial infarction (usually causing focal, not diffuse, uptake), diffuse myocardial scarring (observed in chronic renal disease and mitral valve calcification), overlying previous rib facture, blood pool (which can be distinguished with SPECT imaging), hydroxychloroquine toxicity, and unusual forms of cardiac amyloidosis (apo A1)	Yes*	H/CL ratio ≥1.6 at 1 h[4]

$ indicates lower cost; $$, higher cost; AL-CM, immunoglobulin light chain amyloid cardiomyopathy; apo A1, apolipoprotein A1; ATTR-CM, transthyretin amyloid cardiomyopathy; EF, ejection fraction; H/CL, heart/contralateral chest ratio; HCM, hypertrophic cardiomyopathy; LV, left ventricular; MRI, magnetic resonance imaging; and SPECT, single-photon emission computed tomography.

*In the context of normal serum and urine immunofixation electrophoresis and serum kappa/lambda ratio.

noninvasive diagnosis of ATTR-CM, although the basis for binding to amyloid deposits remains unknown.[16–18] ^{99m}Tc compounds include PYP (pyrophosphate), DPD (3,3-diphosphono-1,2-propanodicarboxylic acid), and hydroxymethylene diphosphonate; PYP is used in the United States. The relative merits of echocardiography, CMR, and ^{99m}Tc-PYP scans are outlined in Table 2.

The testing algorithm shown in Figure 1 begins with a high index of suspicion (Table 1). CMR alone is not diagnostic of ATTR-CM. CMR is the appropriate test when an infiltrative cardiomyopathy is suspected but ATTR-CM is less likely, as in younger patients or those with findings suggestive of other infiltrative/inflammatory or restrictive cardiomyopathies, including

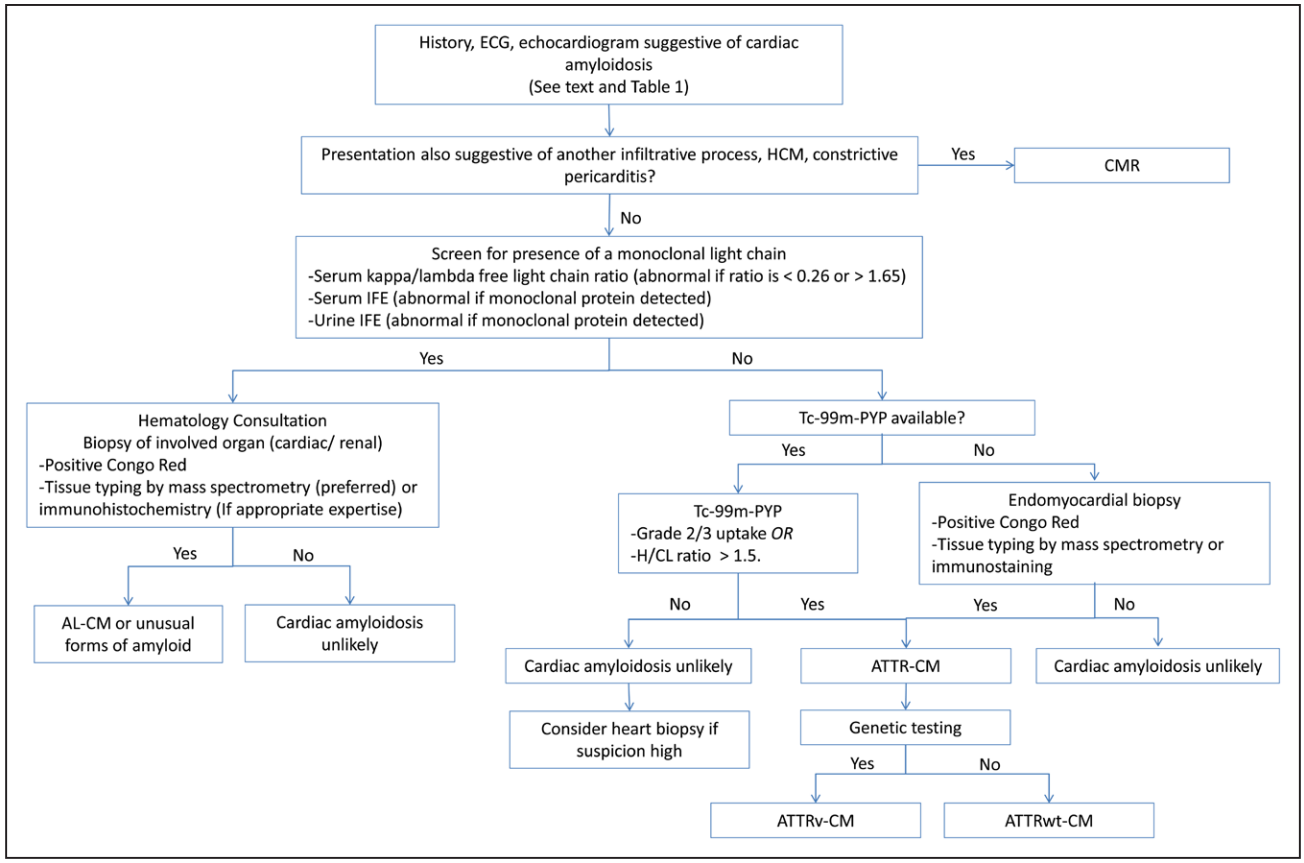

Figure 1. Testing algorithm for transthyretin amyloidosis (ATTR).
Cardiac magnetic resonance imaging is not diagnostic for ATTR cardiomyopathy (CM) but can suggest the diagnosis and is useful when infiltrative cardiomyopathy, constrictive pericarditis, or myocarditis is suspected. Although, practically, screening for the presence of a monoclonal light chain and ^{99m}technetium-pyrophosphate (^{99m}Tc-PYP) scans can be ordered together for convenience, the results of the ^{99m}Tc-PYP scan should be interpreted only in the context of a negative monoclonal light chain screen. Single-photon emission computed tomography imaging is required if there is grade 1 or higher ^{99m}Tc-PYP to distinguish blood pool from myocardial retention. Note that mild elevations in the serum free light chain kappa/lambda ratio frequently occur in patients with renal disease, and in the setting of normal immunofixation, a kappa/lambda ratio of up to 3.0 can be normal.[21] Consultation with a hematologist can be considered in such circumstances. AL indicates immunoglobulin light chain; ATTRv, cardiac variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CMR, cardiac magnetic resonance; H/CL, heart/contralateral chest ratio; HCM, hypertrophic cardiomyopathy; and IFE, immunofixation electrophoresis.

sarcoidosis, hemochromatosis, or Fabry disease, as well as hypertrophic cardiomyopathy, myocarditis, or constrictive pericarditis.[22]

Although bone scintigraphy has emerged as a cornerstone of ATTR-CM diagnosis, scans may be positive even in AL amyloidosis,[18] and a bone scintigraphy scan alone, without concomitant testing for light chains, is neither appropriate nor valid for distinguishing ATTR-CM from AL amyloid cardiomyopathy (AL-CM).

Serum free light chain concentration and serum and urine immunofixation electrophoresis (IFE) are assessed to rule out AL-CM. Serum plasma electrophoresis testing and urine plasma electrophoresis testing are less sensitive and should be avoided. The sensitivity of serum plasma electrophoresis for AL amyloidosis is ≈70%, whereas the sensitivity of serum IFE is >90%.[23] Together, measurement of serum IFE, urine IFE, and serum free light chain is >99% sensitive for AL amyloidosis.[24,25]

Assessment of ATTR-CM with bone scintigraphy is accomplished by semiquantitative or quantitative approaches (Figure 2). The semiquantitative grading involves comparing heart to rib uptake: grade 0 is no cardiac and normal rib uptake; grade 1 is cardiac less than rib uptake; grade 2 is cardiac equal to rib uptake; and grade 3 is cardiac greater than rib uptake with mild/absent rib uptake. Quantitative analysis involves comparison of mean counts as determined by a region of interest placed over the heart and compared with a similar-sized region of intensity placed over the contralateral chest. In the absence of a light chain abnormality, the ^{99m}Tc-PYP scan is diagnostic of ATTR-CM if there is grade 2 to 3 cardiac uptake or a heart/contralateral chest ratio >1.5. Single-photon emission computed tomography is assessed in all positive scans to confirm that uptake represents myocardial retention of the tracer, not blood pool signal.[4]

Although the presence of grade 2 or 3 scintigraphic uptake has a high specificity in amyloid centers with

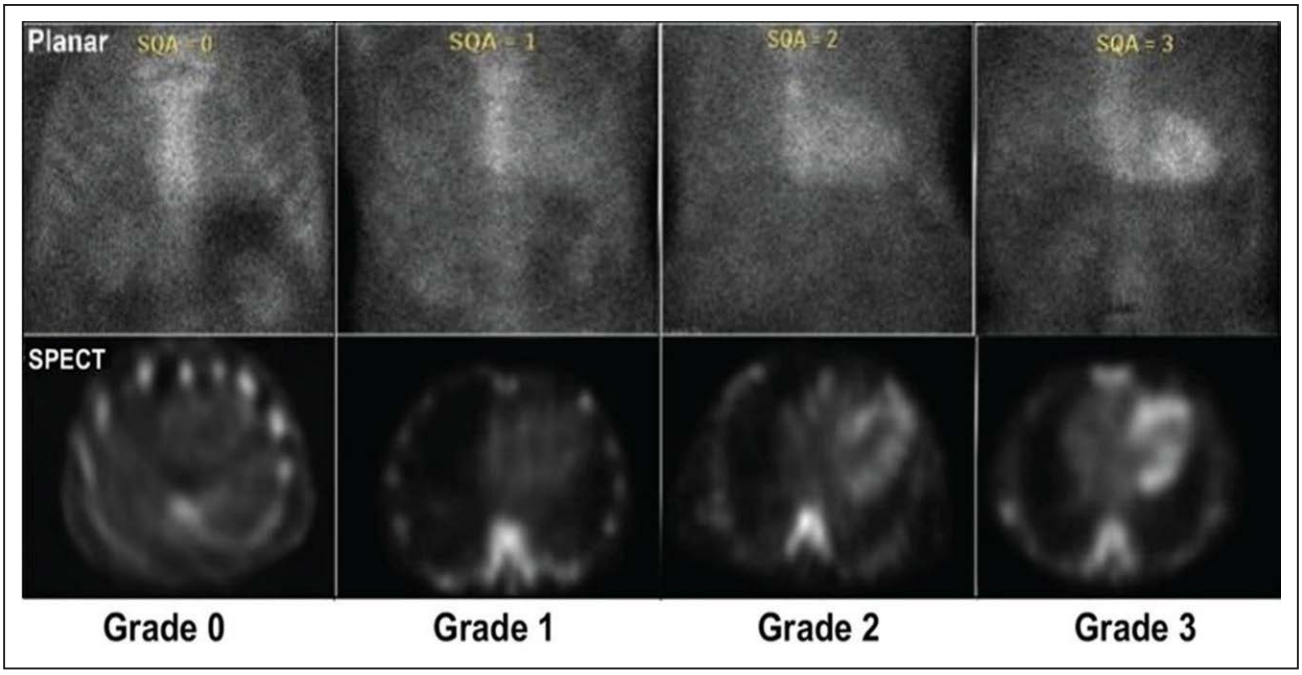

Figure 2. ^{99m}Technetium-pyrophosphate imaging for transthyretin cardiac amyloidosis.
Single-photon emission computed tomography (SPECT) imaging to identify myocardial retention of technetium-based isotopes is useful in discriminating blood pool on planar scans that result in a false-positive test from myocardial uptake of the isotope indicative of transthyretin amyloidosis with cardiomyopathy. SQA indicates semiquantitative analysis. Reprinted from Maurer et al.[26] Copyright © 2019, American Heart Association, Inc. Source figure adapted from Bokhari et al[27] with permission of the American Society of Nuclear Cardiology. Copyright © 2016, American Society of Nuclear Cardiology.

a high prevalence of ATTR-CM, the test performance in populations with lower disease prevalence is unknown. The causes of false-positive ^{99m}Tc-PYP scans are shown in Table 2.

In some situations, endomyocardial biopsy may be necessary to establish the diagnosis: (1) a positive ^{99m}Tc-PYP scan and evidence of a plasma cell dyscrasia by serum/urine IFE or serum free light chain analysis to exclude AL-CM (because AL-CM and ATTR-CM may very rarely occur together in the same patient, such that patients with biopsy-proven AL-CM, especially if older, may also have superimposed ATTRwt-CM deposits); (2) a negative or equivocal ^{99m}Tc-PYP scan despite a high clinical suspicion to confirm ATTR-CM; and (3) unavailability of ^{99m}Tc-PYP scanning. Given its low sensitivity, a fat-pad biopsy is not sufficient to exclude ATTR-CM.[28]

If ATTR-CM is identified, then genetic sequencing of the *TTR* gene is required to define ATTRv versus ATTRwt disease (Table 3). Differentiating ATTRv from ATTRwt is critical because confirmation of ATTRv should trigger genetic counseling and potential screening of family members; the identification of the Val122Ile mutation suggests aggressive progression meriting closer follow-up; and certain therapies are currently approved only for ATTRv. Neurological consultation should be pursued if neurological involvement is present or suspected or if the identified mutation is associated with neurological involvement. Note that age alone is not a valid discriminator of ATTRwt versus ATTRv disease. Two staging schemes offer prognostic insight into ATTR-CM (Table 4).

OVERVIEW OF DISEASE-MODIFYING THERAPIES FOR ATTR-CM

Targets for disease-modifying therapies in cardiac amyloidosis include TTR silencing, TTR stabilization, and TTR disruption (Figure 3 and Table 5). TTR stabilizers bind to the TTR tetramer and prevent misfolding and thus deposition of amyloid fibrils. TTR silencers target TTR hepatic synthesis. TTR disruptors target the clearance of amyloid fibrils from tissues.

TTR Silencing

TTR protein silencers target the hepatic synthesis of TTR. Patisiran is an intravenously administered siRNA that degrades TTR mRNA, and inotersen is a subcutaneously administered single-stranded antisense oligonucleotide that binds TTR mRNA, leading to degradation. Both therapies result in >85% reduction in circulating TTR protein concentration.

Two randomized trials of TTR silencers in patients with ATTRv amyloidosis and polyneuropathy have been reported: the APOLLO trial (A Study to Evaluate Patisiran in Participants With Transthyretin Amyloidosis With Cardiomyopathy; patisiran)[35] and NEURO-TTR (Efficacy and Safety of Inotersen in

Table 3. Common Genotypes in ATTR-CM

	Age at Onset, y	Sex Distribution	National/Ethnic Predominance	Cardiac Involvement	Other Organ Involvement
Val30Met (V30M) or pV50M	<30 in early onset >60 in late onset	Slight F>M	Portuguese, Swedish, and Japanese	Conduction disease more common than heart failure	Peripheral neuropathy Autonomic neuropathy
Val122Ile (V122I) or pV142I	60–65 (older age at onset in women)	Slight M>F	Afro-American Afro-Caribbean	Common	Peripheral neuropathy likely Bilateral carpal tunnel syndrome
Thr60Ala (T60A) or pT80A	>60	Unknown	Irish	Common	Autonomic and peripheral neuropathy
TTRwt	70–75	80%–90% male	None	Common	Bilateral carpal tunnel syndrome, spinal stenosis, biceps tendon rupture

ATTR-CM indicates transthyretin amyloid cardiomyopathy; and TTRwt, wild-type transthyretin.
Data derived from Lane et al,[3] Maurer et al,[11] Connors et al,[29] Lopes et al,[30] and Sattianayagam et al.[31]

Familial Amyloid Polyneuropathy; inotersen).[36] Both demonstrated slower progression of amyloidosis-related polyneuropathy.

Although not explicitly tested, there is evidence that TTR silencers may have beneficial cardiac effects. Prespecified subgroup analyses of APOLLO trial participants with increased LV wall thickening unrelated to hypertension or aortic stenosis (assumed to be from amyloidosis) demonstrated that patisiran attenuated the deterioration of LV global longitudinal strain,[38] LV wall thickness, and NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentration.[39] Similarly, inotersen demonstrated stabilization of LV wall thickness, 6-minute walk test, and global systolic strain.[40] Trials to assess the efficacy of TTR silencers in ATTR-CM are ongoing: APOLLO-B (A Study to Evaluate Patisiran in Participants With Transthyretin Amyloidosis With Cardiomyopathy [ATTR Amyloidosis With Cardiomyopathy]; URL: ClinicalTrials.gov. Unique identifier: NCT03997383; patisiran), 24 Month Open Label Study of the Tolerability and Efficacy of Inotersen in TTR Amyloid Cardiomyopathy Patients (URL: ClinicalTrials.gov. Unique identifier: NCT03702829; inotersen), HELIOS-B (A Study to Evaluate Vutrisiran in Patients With Transthyretin Amyloidosis With Cardiomyopathy; URL: ClinicalTrials.gov. Unique identifier: NCT04153149; vutrisiran), and CARDIO-TTRansform (A Study to Evaluate the Efficacy and Safety of AKCEA-TTR-LRx in Participants With TransthyretinMediated Amyloid Cardiomyopathy [ATTR CM]; URL: ClinicalTrials.gov. Unique identifier: NCT04136171; AKCEA-TTR-LRx).

Table 4. Prognostic Staging Systems for ATTR-CM

	Mayo Staging System[1]	UK Staging System[2]
Population	ATTRwt-CM	ATTRv-CM and ATTRwt-CM
Parameters	Troponin T ≤0.05 ng/mL NT-proBNP ≤3000 pg/mL	NT-proBNP ≤3000 pg/mL eGFR ≥45 mL/min
Median survival		
Stage 1: both parameters normal	66 mo	69.2 mo
Stage 2: 1 parameter abnormal	40 mo	46.7 mo
Stage 3: both parameters abnormal	20 mo	24.1 mo

ATTR-CM indicates transthyretin amyloid cardiomyopathy; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; eGFR, estimated glomerular filtration rate; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

TTR Stabilization

Diflunisal is a nonsteroidal anti-inflammatory that stabilizes TTR in vitro. In a randomized trial of patients with ATTRv and polyneuropathy, diflunisal was associated with reduced progression of polyneuropathy.[34] There are no controlled trials of diflunisal in patients with ATTR-CM, although single-center retrospective analyses demonstrate safety and tolerability and suggest efficacy.[41,42]

Tafamidis is a TTR stabilizer that binds the thyroxine-binding site of TTR. In the ATTR-ACT randomized trial (Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy) of patients with ATTRwt-CM or ATTRv-CM, tafamidis was associated with a significantly lower all-cause mortality (29.5% versus 42.9%) and lower cardiovascular-related hospitalization (0.48 versus 0.70 per year) after 30 months. There was a higher rate of cardiovascular-related hospitalizations in the prespecified subgroup of patients with NYHA class III heart failure, which may have been attributable to longer survival during a more severe period of disease, underscoring the importance of early diagnosis and treatment. Tafamidis was also associated with a lower rate of decline in 6-minute walk distance ($P<0.001$) and a lower rate of decline in Kansas City Cardiomyopathy Questionnaire-Overall Summary score ($P<0.001$).[33] Tafamidis was approved by the US Food and Drug Administration for use in ATTR-CM in May 2019.

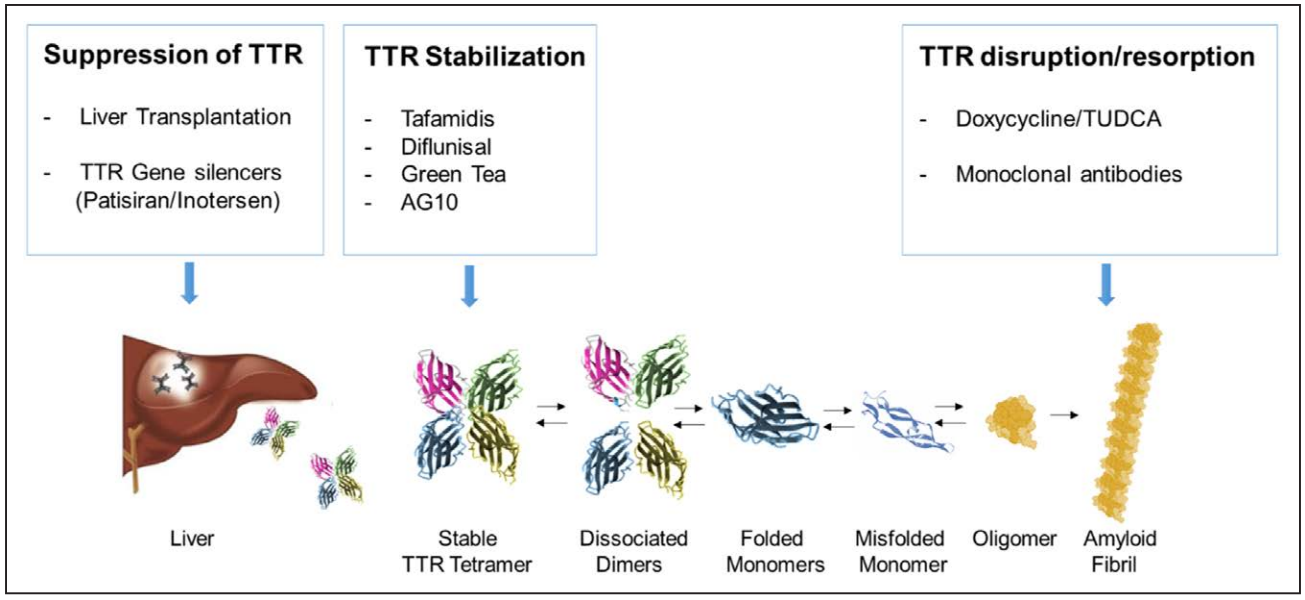

Figure 3. TTR (transthyretin) production and targets of therapy.
Inherited mutations in cardiac variant transthyretin amyloidosis (ATTRv) or the aging process in wild-type disease (ATTRwt) cause destabilization of the TTR protein into monomers or oligomers, which aggregate into amyloid fibrils. These insoluble fibrils accumulate in the myocardium and result in diastolic dysfunction, restrictive cardiomyopathy, and eventual congestive heart failure. Targets of therapy include TTR production (silencers), TTR dissociation (TTR stabilizers), and TTR clearance from tissues (TTR disruption). TUDCA indicates tauroursodeoxycholic acid. Adapted from Nativi-Nicolau and Maurer[32] with permission. Copyright © 2018, Wolters Kluwer Health, Inc.

AG10 is a TTR stabilizer that binds to the tetramer and mimics coinheritance of the *TTR* T119M mutation, providing natural stabilization of TTR to prevent amyloid fibril formation and deposition. A phase 2 trial of AG10 demonstrated an acceptable safety profile,[43] and data from the open-label extension indicate that mortality and cardiovascular hospitalization were lower in AG10 open-label extension participants than in placebo-treated ATTR-ACT participants at 15 months.[44] A phase 3 trial of AG-10 is in progress (ATTRIBUTE-CM [Efficacy and Safety of AG10 in Subjects With Transthyretin Amyloid Cardiomyopathy]; URL: ClinicalTrials.gov. Unique identifier: NCT03860935).

TTR Disruption/Resorption

TTR disruption targets the clearance of amyloidosis fibrils from tissues. Preclinical studies demonstrated that doxycycline plus TUDCA (tauroursodeoxycholic acid) removed amyloid deposits. However, small open-label studies demonstrated a high incidence of side effects with conflicting results on efficacy.[45,46] EGCG (epigallocatechin-3-gallate), a catechin in green tea, inhibits amyloid fibril formation in vitro, but there is little evidence of benefit[47] from it or turmeric. With the advent of US Food and Drug Administration–approved therapies, the therapeutic roles of these agents are uncertain. Other agents, including monoclonal antibodies such as PRX004, are under investigation.[48]

APPROACH TO TREATMENT IN CARDIAC AMYLOIDOSIS

As outlined in Figure 4, treatment of cardiac amyloidosis focuses on 3 areas: management of heart failure, management of arrhythmias, and initiation of disease-modifying agents.

Management of Heart Failure

The physiology of restrictive LV filling and reduced stroke volume/cardiac output in cardiac amyloidosis renders volume maintenance difficult. Bioavailable 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. Aldosterone antagonists may be used alone or in conjunction with loop diuretics in patients with adequate blood pressure and renal function.

There are no data supporting the use of standard guideline-directed medical therapy for heart failure with reduced ejection fraction or HFpEF in ATTR-CM, including angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, or angiotensin receptors blockers–neprilysin inhibitors. Furthermore, these therapies may exacerbate hypotension when amyloid-associated autonomic dysfunction is present.

β-Blockers and nondihydropyridine calcium channel blockers are often poorly tolerated, even at low

Table 5. Summary of Disease-Modifying Agents Currently Available for ATTR

Drug	Indication/ Approval	Dose/Delivery	Clinical Trial Key Inclusion/Exclusion	Potential Side Effects	Monitoring	Average Wholesale Price
TTR stabilizers						
Tafamidis	FDA approved for ATTRwt-CM and ATTRv-CM	20, 61, or 80 mg once daily	ATTR-ACT trial[33] Inclusion: End-diastolic septal thickness >12 mm History of heart failure NT-proBNP ≥600 pg/mL Exclusion: 6MWT <100 m NYHA class IV symptoms Liver or heart transplantation eGFR <25 mL·min^{-1}·1.73 m^{-2}	Potentially more gastrointestinal upset than placebo on 61 mg	None	$225 000/y
Diflunisal	FDA approved as NSAID Off-label use in ATTRwt or ATTRv with neuropathy/ cardiomyopathy	250 mg orally twice daily Administer with proton pump inhibitor	Diflunisal Trial Consortium[34] Inclusion: ATTRv with sensorimotor polyneuropathy (familial amyloid polyneuropathy) Biopsy-proven amyloid deposits Confirmed *TTR* mutation Exclusion: NYHA class IV symptoms Estimated creatinine clearance <30 mL/min* Anticoagulation	Fluid retention Renal dysfunction Bleeding	Renal function Platelet count Hemoglobin	≈$60/mo
TTR silencers						
Patisiran	FDA approved for ATTRv with neuropathy	0.3 mg/kg intravenously every 3 wk Premedication with intravenous corticosteroids, intravenous H1 blocker, H2 blocker Daily vitamin A supplement	APOLLO Trial[35] Inclusion: Documented *TTR* mutation Confirmed ATTRv with polyneuropathy (familial amyloid polyneuropathy) NIS score 5–130 PND score ≤3b Exclusion: NYHA class III–IV symptoms Liver transplantation	Infusion-related reactions Vitamin A deficiency	None	$414 162/y†
Inotersen	FDA approved for ATTRv with neuropathy	284 mg/wk subcutaneously Daily vitamin A supplement	NEURO-TTR Trial[36] Inclusion: ATTRv with polyneuropathy (familial amyloid polyneuropathy) stage 1 and 2 familial amyloid polyneuropathy NIS ≥10 and ≤130 Documented TTR mutation Documented amyloid deposit on biopsy Exclusion: Platelets <125×10^9/L Creatinine clearance <60 mL·min^{-1}·1.73 m^{-2} NYHA class III symptoms Liver transplantation	Thrombocytopenia Glomerulonephritis Infusion-related reactions Vitamin A deficiency	Weekly platelet count Every 2 wk, serum creatinine, eGFR, and UPCR	$359 840/y

6MWT indicates 6-minute walk test; APOLLO, A Study to Evaluate Patisiran in Participants With Transthyretin Amyloidosis With Cardiomyopathy; ATTR, transthyretin amyloidosis; ATTRv, cardiac variant transthyretin amyloidosis; ATTRv-CM, variant transthyretin amyloid cardiomyopathy; ATTRwt, wild-type transthyretin amyloidosis; ATTRwt-CM, wild-type transthyretin amyloid cardiomyopathy; ATTR-ACT, Safety and Efficacy of Tafamidis in Patients With Transthyretin Cardiomyopathy; CM, cardiomyopathy; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; NEURO-TTR, Efficacy and Safety of Inotersen in Familial Amyloid Polyneuropathy; NIS, Neuropathy Impairment Score; NSAID, nonsteroidal anti-inflammatory drug; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PND, polyneuropathy disability; TTR, transthyretin; and UPCR, urine protein to creatinine ratio.

*In clinical practice, tafamidis is not suggested for patients with creatinine clearance <45 mL/min.

†Average wholesale price of patisiran based on a patient weight of 70 kg and does not include the price of premedication or infusion-related expenses. Average wholesale prices taken from Micromedex online database.[37]

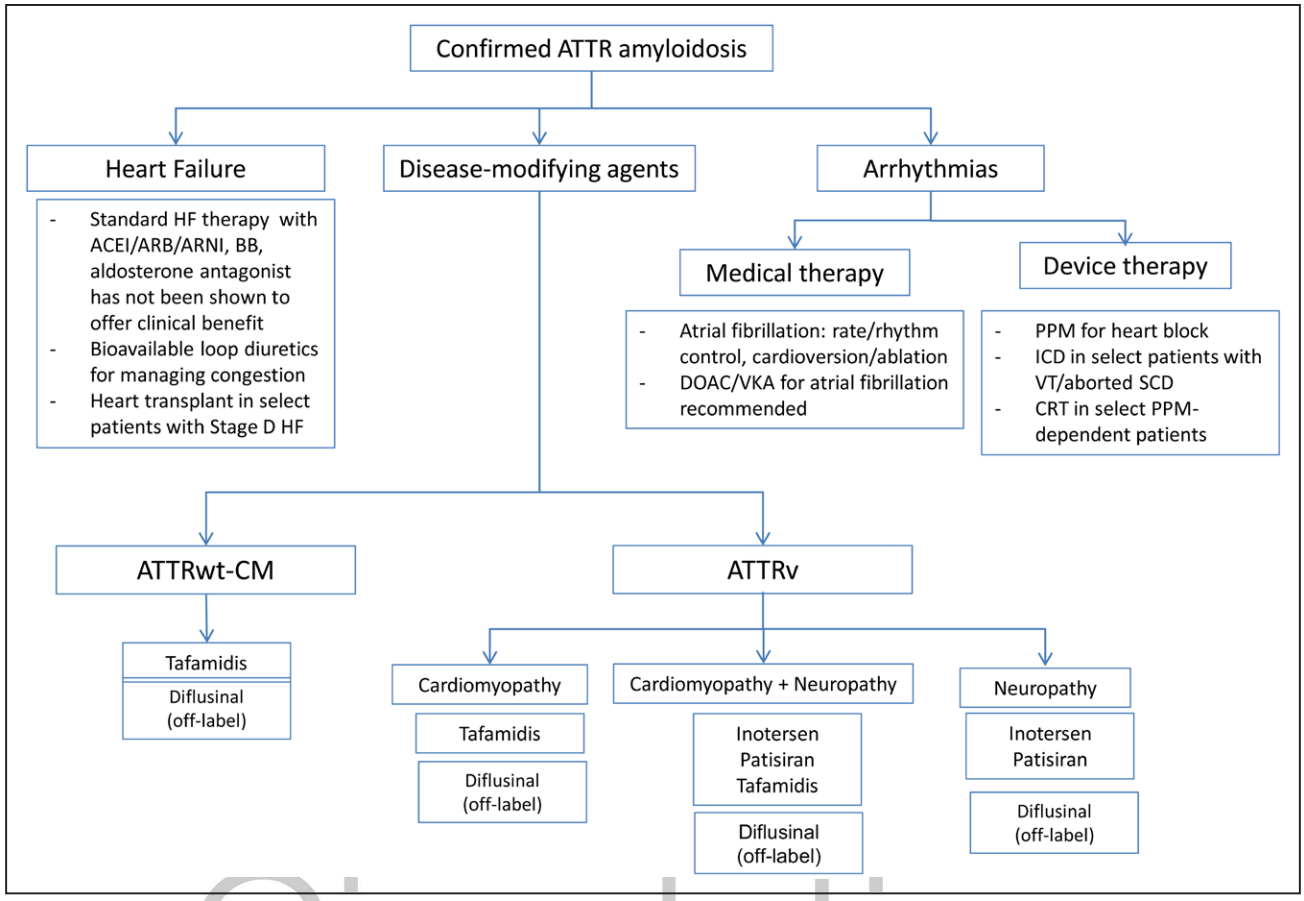

Figure 4. Treatment algorithm for transthyretin amyloidosis (ATTR).
ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor blocker–neprilysin inhibitor; ATTRv, cardiac variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; BB, β-blocker; CM, cardiomyopathy; CRT, cardiac resynchronization therapy; DOAC, direct oral anticoagulant; HF, heart failure; ICD, implantable cardioverter-defibrillator; PPM, permanent pacemaker; SCD, sudden cardiac death; VKA, vitamin K antagonist; and VT, ventricular tachycardia.

doses, because patients with ATTR-CM rely on heart rate response to maintain cardiac output given a fixed stroke volume. In AL amyloidosis, nondihydropyridine calcium channel blockers also bind amyloid fibrils and can result in heart block or shock.

Management of Arrhythmias

Amyloid cardiomyopathy is associated with atrial dysfunction and both atrial and ventricular arrhythmias. Atrial dysfunction may be reflected by decreased A-wave amplitude and left atrial appendage velocities on echocardiography, and in such cases, empirical anticoagulation may be warranted even in sinus rhythm.[49] There is no definitive reported comparison of warfarin and direct oral anticoagulants to prevent thromboembolism in this setting.

As a result of atrial dysfunction in ATTR-CM, anticoagulation is indicated for atrial fibrillation/flutter regardless of CHA_2DS_2-VASc score. Left atrial appendage closure devices have not been studied in ATTR-CM but may be considered in patients with prohibitive bleeding risk. Digoxin may be used cautiously for rate control, although there is concern about potential digoxin toxicity caused by binding of digoxin to amyloid fibrils. Amiodarone is the agent of choice for both rhythm and rate control, particularly in cases in which β-blockade is not tolerated; cardioversion and ablation should also be considered in selected cases.

Because of the high incidence of conduction system disease from amyloid infiltration, ambulatory electrocardiographic monitoring is part of the syncope evaluation, and pacemakers are indicated per Heart Rhythm Society consensus guidelines.[50] Implantable cardioverter-defibrillators (ICDs) are recommended in cases of aborted sudden cardiac death with expected survival >1 year or significant ventricular arrhythmias. However, the benefit of ICDs, particularly for primary prevention of sudden cardiac death, is questionable. In a study of 45 patients with amyloid cardiomyopathy (32 with ATTR-CM), an ICD was placed for primary prevention in 38 of the patients. Over follow-up, 12% of patients had at least 1 appropriate ICD therapy; no clinical characteristics predicted who would receive ICD therapy.[51] On the basis of limited experience, although Heart Rhythm Society guidelines assign a Class IIb indication to ICD placement in AL-CM and nonsustained ventricular tachycardia with expected survival >1 year, the use of ICDs for primary prevention of sudden

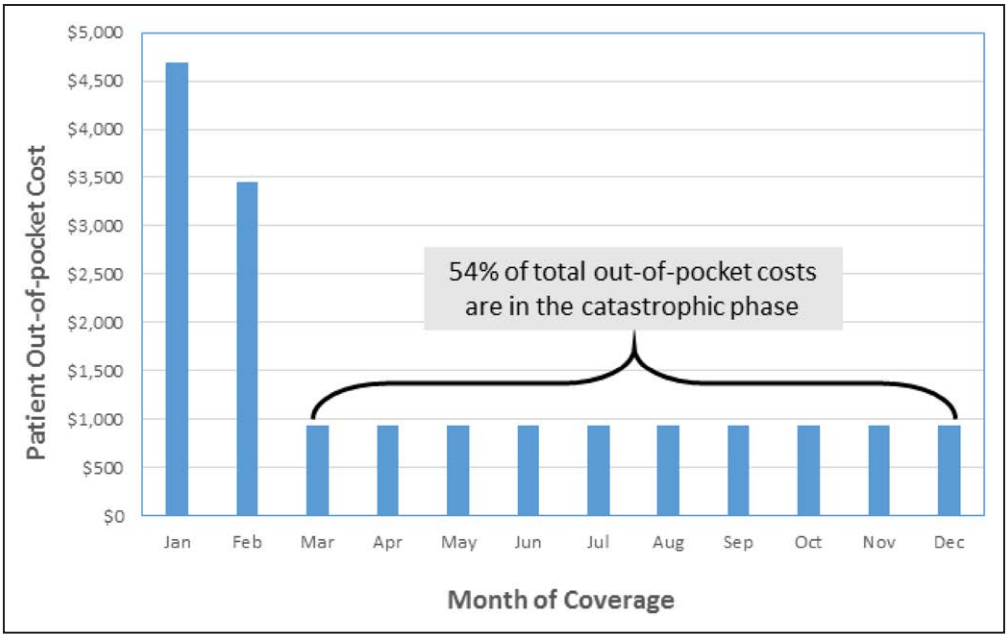

Figure 5. Projected Medicare Part D beneficiary monthly out-of-pocket costs for tafamidis.
Projected annual out-of-pocket expenses were calculated using the standard 2019 Medicare Part D plan including: (1) an initial $415 deductible; (2) an initial coverage period until drug costs reach $3810; (3) a coverage gap ("donut hole") with 25% cost sharing until out-of-pocket costs reach $5100; and (4) catastrophic coverage with 5% cost sharing without an upper limit. Monthly insurance premiums and the costs of other medications were not included in this projection.

cardiac death in patients with ATTR-CM is not well established.[52] Cardiac resynchronization therapy may be useful in pacemaker-dependent patients because the already depressed stroke volume may worsen with long-term right ventricular pacing.[53]

Implementation of Disease-Modifying Therapies in ATTR-CM

The use of US Food and Drug Administration–approved disease-modifying therapy is based on the presence of cardiomyopathy and polyneuropathy and the distinction between ATTRv and ATTRwt amyloidosis (Figure 5). In patients with predominantly cardiac disease resulting from ATTRv or ATTRwt, tafamidis is indicated in those with NYHA class I to III symptoms,[33] and early initiation appears to slow disease progression. The benefit of tafamidis has not been observed in patients with class IV symptoms, severe aortic stenosis, or impaired renal function (glomerular filtration rate <25 mL·min^{-1}·1.73 m^{-2} body surface area).

Patients with ATTRv and polyneuropathy should be considered for TTR silencing therapy with patisiran[35] or inotersen[36]; currently, neither is indicated for ATTRv-CM without polyneuropathy or in ATTRwt-CM. In patients with ATTRv-CM with polyneuropathy, the choice between therapeutic agents is based on accessibility and side-effect profile.

The use of combination therapies is appealing to synergistically target both TTR silencing and stabilization of the remaining synthesized protein, but this approach lacks data and may be cost-prohibitive.

Diflusinal (250 mg orally twice daily) may be considered with caution for off-label therapy for asymptomatic ATTR carriers, for patients with ATTR-CM who are not eligible for TTR silencers, or for patients with ATTR-CM who are intolerant of or cannot afford tafamidis. Because of the nonsteroidal anti-inflammatory properties, close monitoring is needed, and diflunisal is contraindicated in patients with significant thrombocytopenia and renal dysfunction (glomerular filtration rate <40 mL·min^{-1}·1.73 m^{-2}) and should be used cautiously in patients on anticoagulation or with a history of gastrointestinal bleeding.

Advanced Heart Failure Therapies in ATTR-CM

For patients with ATTR-CM with stage D heart failure, use of an LV assist device is challenging because of the small LV cavity size and concomitant right ventricular dysfunction.[54] There are limited data to support considering the total artificial heart as a bridge to transplantation in patients without significant extracardiac disease.[55]

Heart transplantation may be considered in patients with stage D heart failure,[56] and the current adult donor allocation system provides priority as status 4 to amyloid cardiomyopathy given the lack of durable mechanical circulatory support options. Generally, heart-liver transplantation is performed in patients with ATTRv-CM at risk for neuropathy because neuropathy may progress with heart transplantation alone, although the criteria for heart alone versus heart-liver transplantation are not well defined,[57] especially with the advent of silencer therapy,

which may have a role after heart transplantation. Liver transplantation alone in ATTRv would offer prohibitive risk in the presence of severe cardiac dysfunction, and preexisting cardiac dysfunction can progress despite subsequent synthesis of wild-type TTR by the donor liver.

AREAS OF UNCERTAINTY AND FUTURE INVESTIGATION

Despite advances in the management of ATTR-CM, areas of uncertainty remain in screening, disease progression, role of TTR silencers in patients with ATTR-CM, timing of therapy initiation, and financial burden of new therapies (Table 6).

Identifying Populations for Screening

Given that the prevalence of cardiac amyloidosis is increased in specific populations (patients with HFpEF, individuals of West African descent, those with small-fiber polyneuropathy), more active ascertainment or screening may be indicated[10] because early identification can maximize the benefit of therapy and delayed diagnosis results in worse outcomes. However, much is not known: the natural history of subclinical TTR cardiac amyloidosis, how testing will perform in groups with lower pretest probability, and the cost-effectiveness of screening.

Biomarkers such as NT-proBNP and troponin, electrocardiography, and echocardiography have low sensitivity/specificity for ATTR-CM. More specific testing may involve measurement of circulating RBP4 (retinol binding protein 4) or misfolded TTR oligomers; both discriminate patients with ATTRv from those with nonamyloid HF and healthy control subjects.[58,59]

Because HFpEF disproportionately affects older blacks and Hispanics compared with whites, there is currently a recruiting National Institutes of Health–funded prospective cohort study using ^{99m}Tc-PYP imaging and measurement of RBP4 and misfolded TTR oligomers to detect ATTR-CM in minority subjects with heart failure (SCAN-MP [Screening for Cardiac Amyloidosis Using Nuclear Imaging for Minority Populations]; URL: ClinicalTrials.gov. Unique identifier: NCT03812172). Other screening studies are ongoing in Afro-Caribbean individuals with increased wall thickness (Frequency of Cardiac Amyloidosis in the Caribbean's [TEAM Amylose]; URL: ClinicalTrials.gov. Unique identifier: NCT03322319), HFpEF patients with increased wall thickness (Transthyretin Cardiac Amyloidosis in HFpEF; URL: ClinicalTrials.gov. Unique identifier: NCT03414632), and those with small-fiber polyneuropathy using *TTR* gene sequencing (Screening for the Transthyretin-Related Familial Amyloidotic Polyneuropathy [TTR FAP]; URL: ClinicalTrials.gov. Unique identifier: NCT01705626). Last, large-scale biobank genotype studies hold promise for determining the prevalence of *TTR* mutations among target populations.

Another area of significant uncertainty is monitoring in asymptomatic carriers of *TTR* mutations.[60] Given the

Table 6. Areas of Active Investigation and Uncertainty in Diagnosis, Prognosis, Progression, and Treatment

Diagnosis
Should we screen for ATTR-CM? If so, in which populations?
Which diagnostic tests should be used for screening?
Are there biomarkers that can raise suspicion of ATTR-CM with sufficient diagnostic certainty to be used for screening?
Which noninvasive test has the best sensitivity for diagnosis of ATTR-CM?
How does bone scintigraphy perform as a screening test (eg, in populations with a lower prevalence of disease than specialized amyloid centers)?
What is the cost-effectiveness of screening or active ascertainment?
How should asymptomatic allele carriers of *TTR* mutations be followed up for disease penetrance?
Prognosis
What is the best combination of prognostic variables in ATTR-CM?
Which biomarkers are most effective for following up patients with ATTR-CM?
What is the role of imaging in ATTR-CM for prognostication?
How does one determine whether a patient with ATTR-CM is progressing on therapy?
What is the role of defibrillators and pacemakers in patients with ATTR-CM?
Progression of disease
How should one measure disease progression?
Do the various domains (eg, QOL, functional measures, biomarkers, imaging) progress at the same rate?
Is there an early marker of disease progression?
Are there biological processes (TTR stability, TTR kinetics or levels, or TTR ligands) that can be used to monitor progression?
Can disease progression inform the choice of therapies and when to change therapies?
Can TTR amyloidosis be reversed? If so, what factors predict regression?
Treatment
How do the efficacies of stabilizers and silencers compare? Do TTR stabilizers differ in efficacy and side-effect profile?
Is combination therapy with TTR stabilizers or silencers additive, synergistic, or not beneficial?
In what order should TTR therapies be administered?
How does the cost of therapy influence adherence, treatment, and outcomes?
Does the cost of therapy affect the development of novel therapies?
When should ATTR-specific therapy be initiated in patients with ATTR-CM?
When should patients with ATTR-CM be considered for advanced surgical heart failure therapies such as LVAD and cardiac transplantation?

ATTR indicates transthyretin amyloidosis; ATTR-CM, transthyretin amyloid cardiomyopathy; LVAD, left ventricular assist device; QOL, quality of life; and TTR, transthyretin.

age-dependent penetrance, the general consensus is to begin assessment 10 years before the affected proband's age at disease onset, although this approach is limited by the unclear natural history of disease. Assessment can include physical examination, electrocardiography, echocardiography, bone scintigraphy, or CMR imaging.[61]

Assessing the Progression of Disease

There is no accepted definition of progression or response to therapy of ATTR-CM, but several measures have been proposed: survival, hospitalizations, functional capacity (NYHA class, 6-minute walk test, gait speed, cardiopulmonary exercise stress testing), quality of life, and cardiac biomarkers and imaging (echocardiography, magnetic resonance imaging, or positron emission tomography).

Currently, the role of imaging modalities in evaluating response to therapy is not established. Each imaging modality has a different sensitivity for detecting the burden of amyloid fibril deposition, varying capacity to quantify deposition, and therefore different ability to identify progression or improvement. Decreasing levels of misfolded TTR may reflect response to therapy,[59] but the role of surveillance imaging and laboratories in assessing response to or guiding changes in therapy requires further study.

Role of TTR Silencers in ATTR-CM Without Neuropathy

Although it is biologically plausible that TTR silencers such as inotersen and patisiran could improve outcomes in ATTR-CM, such conclusions must await the results of adequately powered clinical trials. As a cautionary example, a subcutaneous RNA interference agent similar to patisiran, revusiran, was associated with increased mortality compared with placebo in ATTRv-CM in the ENDEAVOUR clinical trial (Phase 3 Multicenter Study of Revusiran [ALN-TTRSC] in Patients With Transthyretin [TTR] Mediated Familial Amyloidotic Cardiomyopathy [FAC]; URL: ClinicalTrials.gov. Unique identifier: NCT02319005).

Timing of Initiation of Disease-Modifying Agents

Given the lack of consensus on defining disease onset in carriers of *TTR* mutations and what methods (imaging or biomarkers) should be used to monitor disease progression, the timing of initiation of therapy in ATTRv carriers remains an area of uncertainty.

In contrast, in patients with advanced disease, treatment aimed at TTR stabilization is unlikely to be of significant benefit. Although the package label for tafamidis does not provide restrictions on administration, patients with NYHA class IV symptoms, minimally ambulatory patients (walk <100 m on a 6-minute walk test), and those with advanced renal dysfunction (estimated glomerular filtration rate <25 mL·min^{-1}·m^{-2}) were ineligible for inclusion in ATTR-ACT. Thus, tafamidis is not suggested for patients with advanced heart failure.

Financial Impact of Disease-Modifying Agents

Significantly affecting equitable prescription of these therapies is their considerable cost, especially because lifelong treatment is required, and the financial implication of potentially treating asymptomatic *TTR* mutation carriers is tremendous.

As noted in Table 6, costs are similar to those of new biologics or chemotherapeutic agents. A significant proportion of patients with ATTR-CM in the United States are older adults with Medicare as their primary insurance. Because Medicare does not allow direct-to-consumer drug maker copay assistance programs, these patients can have significant out-of-pocket expenses.[62]

Even with Medicare Part D prescription drug coverage, the average cost of tafamidis could approach $18 000 per year, more than half of which occurs after the catastrophic coverage threshold, and would reset annually for every year of treatment (Figure 5). Despite independent charity assistance foundations, the most common income limit was 500% of the federal poverty level (annual income of $62 450 for an individual and $84 550 for a married couple in 2019).[63] There are a significant number of patients who may fall above such thresholds but for whom this annual out-of-pocket expense would not be feasible on fixed incomes.

Manufacturers have committed to work with insurers and patients to ensure that no one who merits drug is deprived because of cost, but the practice and impact of such commitments have yet to be fully demonstrated, and a cost-effectiveness analysis of tafamidis indicated that the list price would need to be reduced by >90% for it to be cost-effective.[64] Thus, a growing area of concern, for which ATTR-CM is not unique but perhaps emblematic, is the gap between ideal medical therapies and the ability of patients to afford them.

CONCLUSIONS

The landscape for the diagnosis of and therapy for ATTR-CM is rapidly evolving. Readily accessible, accurate, noninvasive diagnostic tests and therapies to improve symptoms and survival are now available. ATTR-CM is no longer accurately regarded as a "zebra" diagnosis. Given the now-recognized clinical relevance of ATTR-CM, clinicians must have a high index of suspicion for cardiac amyloidosis when patients present with clinical clues and should invoke a rational diagnostic algorithm to evaluate for both AL-CM and ATTR-CM. Once the diagnosis is made, differentiating between

ATTRv-CM, ATTRwt-CM, and the presence or absence of neuropathy will allow clinicians to implement an appropriate strategy of heart failure and arrhythmia management along with disease-modifying agents.

Uncertainties exist in screening, the assessment of progression, the management of asymptomatic carriers of ATTRv, the use of TTR silencing agents in ATTR-CM, and the financial impact of disease-modifying therapies. Current and future studies will assess these unanswered knowledge gaps, and advocacy from clinicians at every level may aid in closing the gap between the best medical therapies for ATTR-CM and the ability of patients to afford them.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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*Modest.

†Significant.

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