JAMA | Review

Cardiac Amyloidosis Due to Transthyretin Protein
A Review

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IMPORTANCE Systemic amyloidosis from transthyretin (ATTR) protein is the most common type of amyloidosis that causes cardiomyopathy.

OBSERVATIONS Transthyretin (TTR) protein transports thyroxine (thyroid hormone) and retinol (vitamin A) and is synthesized predominantly by the liver. When the TTR protein misfolds, it can form amyloid fibrils that deposit in the heart causing heart failure, heart conduction block, or arrhythmia such as atrial fibrillation. The biological processes by which amyloid fibrils form are incompletely understood but are associated with aging and, in some patients, affected by inherited variants in the *TTR* genetic sequence. ATTR amyloidosis results from misfolded TTR protein deposition. ATTR can occur in association with normal *TTR* genetic sequence (wild-type ATTR) or with abnormal *TTR* genetic sequence (variant ATTR). Wild-type ATTR primarily manifests as cardiomyopathy while ATTR due to a genetic variant manifests as cardiomyopathy and/or polyneuropathy. Approximately 50 000 to 150 000 people in the US have heart failure due to ATTR amyloidosis. Without treatment, heart failure due to ATTR amyloidosis is associated with a median survival of approximately 5 years. More than 130 different inherited genetic variants in *TTR* exist. The most common genetic variant is Val122Ile (pV142I), an allele with an origin in West African countries, that is present in 3.4% of African American individuals in the US or approximately 1.5 million persons. The diagnosis can be made using serum free light chain assay and immunofixation electrophoresis to exclude light chain amyloidosis combined with cardiac nuclear scintigraphy to detect radiotracer uptake in a pattern consistent with amyloidosis. Loop diuretics, such as furosemide, torsemide, and bumetanide, are the primary treatment for fluid overload and symptomatic relief of patients with ATTR heart failure. An ATTR-directed therapy that inhibited misfolding of the TTR protein (tafamidis, a protein stabilizer), compared with placebo, reduced mortality from 42.9% to 29.5%, reduced hospitalizations from 0.7/year to 0.48/year, and was most effective when administered early in disease course.

CONCLUSIONS AND RELEVANCE ATTR amyloidosis causes cardiomyopathy in up to approximately 150 000 people in the US and tafamidis is the only currently approved therapy. Tafamidis slowed progression of ATTR amyloidosis and improved survival and prevented hospitalization, compared with placebo, in people with ATTR-associated cardiomyopathy.

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Systemic amyloidosis due to accumulation of misfolded transthyretin (TTR) protein causes cardiomyopathy in approximately 50 000 to 150 000 people in the US. TTR, also known as prealbumin, is a circulating protein synthesized by the liver that transports thyroid hormone and the retinol (vitamin A)-binding protein 4 complex.[1] TTR typically exists as a homotetramer, but TTR can dissociate into its constituent subunits that subsequently misfold and aggregate into amyloid fibrils. Amyloidosis results from deposition of misfolded protein fibrils in organs or other body tissues. Nomenclature for amyloidosis uses the letter A followed by an abbreviation of the misfolded protein. Therefore, ATTR is the term used to refer to amyloidosis caused by misfolding of the TTR protein.

ATTR amyloidosis manifests principally as cardiomyopathy and polyneuropathy.[2] Cardiomyopathy due to ATTR amyloidosis can cause heart failure, arrhythmia, and death, while ATTR deposition in nerves causes a small-fiber peripheral and/or autonomic polyneuropathy. ATTR deposition in ligaments manifests as carpal tunnel syndrome and cervical or lumbar spinal stenosis.[3,4] In one form of ATTR amyloidosis (variant ATTR), inherited *TTR* gene variants cause amino acid substitutions promoting amyloidogenesis.[5] In the other form of ATTR amyloidosis, a normal *TTR* genotype (wild-type ATTR) is present without destabilizing *TTR* variants. The mechanisms underlying TTR protein dissociation and amyloid fibril formation are incompletely understood but ATTR amyloidosis is more common in older people.[1] Wild-type ATTR is the most common type of

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Table 1. Genetic Variants Associated With ATTR Amyloidosis in the US

Genotype	Estimated frequency	Estimated penetrance	Typical age at onset, y	Clinical characteristic
Wild-type (no pathological genetic variants)	• 12% (95% CI, 6%-20%) in HFpEF; 10% (95% CI, 6%-15%) in HFrEF • 7% (95% CI, 5%-10%) in surgery for carpal tunnel syndrome • 7% (95% CI, 5%-18%) in hypertrophic cardiomyopathy phenotype • 8% (95% CI, 5%-13%) in severe aortic stenosis • 21% (95% CI, 7%-39%) in autopsy series of "unselected" older individuals[17]	Not genetically inherited	>60	Predominantly cardiac
Val122Ile (also known as V122I or pV142I)	3.4% African American individuals[18]	~7% to 100% >age 60 y, increases with age, males > females[19-21]	>65	Predominantly cardiac
Val30Met (also known as V30M or pV50M, early onset, endemic regions)	Most common worldwide, 4% in northern regions of Sweden, 1:500 northern regions of Portugal[18]	>90%	<50	Predominantly neurologic
Val30Met (late-onset, endemic and nonendemic regions)	1:1 000 000 in Japan and Sweden[18]	>60%	>50	Mixed
Thr60Ala (also known as T60A or pT80A)	1% County Donegal, Republic of Ireland[18]	>90%	>50	Mixed

Abbreviations: ATTR, amyloidosis from transthyretin; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

ATTR amyloidosis (approximately 75% of ATTR amyloidosis) and typically manifests as cardiomyopathy, and fewer than 10% of patients have concurrent polyneuropathy.[6,7] ATTR amyloidosis due to genetic variant(s) affects an unknown number of people. More than 130 gene variants in TTR have been identified. However, a common inherited pathological *TTR* variant exists in more than 1.5 million people in the US, but the proportion of variant carriers who develop clinical manifestations of amyloidosis is not well defined. ATTR due to a genetic variant manifests as either cardiomyopathy with or without coexistent polyneuropathy with a phenotype that depends on the specific variant.[5] This review summarizes the clinical presentation, diagnosis, and treatment of ATTR cardiomyopathy.

Methods

A search of PubMed was performed to identify studies published between January 1, 2000, and January 11, 2024, in the English language related to ATTR cardiomyopathy and therapeutics. Reference lists of selected articles were manually inspected to identify additional relevant references. Higher-quality studies, such as randomized, placebo-controlled, clinical trials and longitudinal observation studies received priority for inclusion. Expert consensus clinical practice guidelines/scientific statements also received priority for inclusion. Of 1282 identified articles, 95 were included, consisting of 57 longitudinal observational studies; 14 randomized clinical trials; 20 practice guidelines, scientific statements, or consensus documents; 2 meta-analyses; and 2 cross-sectional studies that described autopsy findings.

Discussion

Epidemiology

Autopsy studies demonstrated that 25% of hearts from decedents older than 80 years without known heart failure contained wild-type ATTR amyloid deposits and that the prevalence of amyloid deposits was higher among older males (>70 years of age) with heart failure.[8,9] Cohorts have inconsistently demonstrated that wild-type ATTR cardiomyopathy is more common in males. In 2 case series of 229 patients with wild-type ATTR cardiomyopathy referred to specialty treatment centers, 81% to 98% of patients were male.[10,11] In a separate screening study of 120 patients (41% male) older than 60 years hospitalized with heart failure with preserved left ventricular ejection fraction (HFpEF) and an increased wall thickness, 16 patients of ATTR cardiomyopathy were identified, of which 50% were male.[12] Using nuclear scintigraphy to diagnose ATTR cardiomyopathy, wild-type ATTR cardiomyopathy was identified in 12% of hospitalized patients older than 60 years with heart failure, preserved left ventricular (LV) ejection fraction (HFpEF), and an increased cardiac wall thickness; 8% of patients with severe aortic stenosis undergoing valve replacement; 6% of community-dwelling patients with HFpEF; and 8% of patients who were considered to possibly have nonobstructive hypertrophic cardiomyopathy.[12-17]

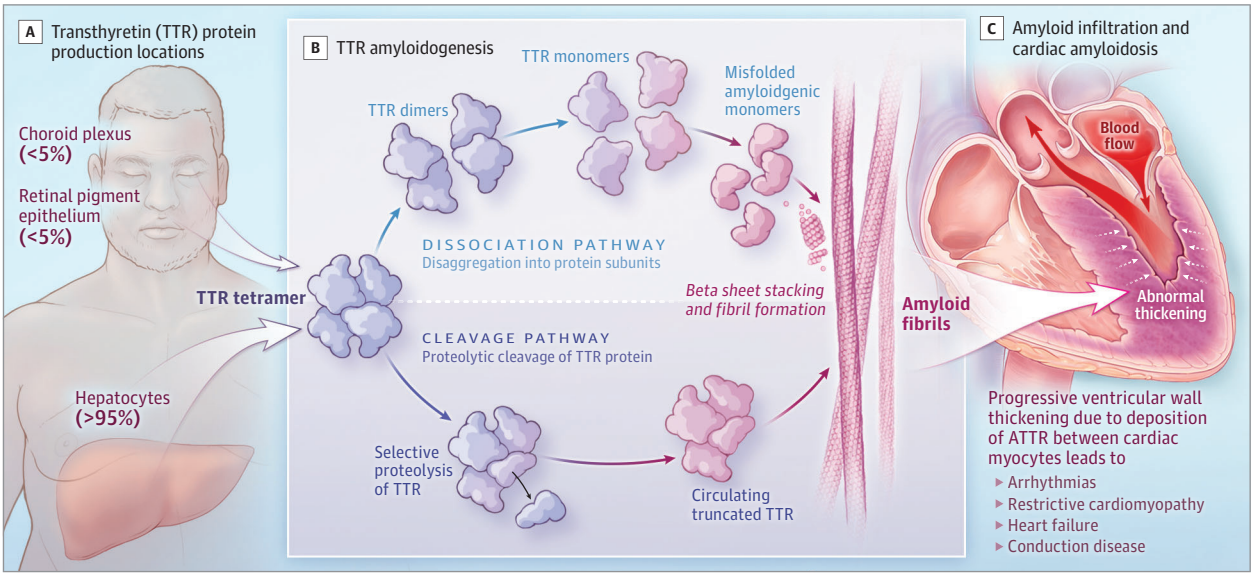
The prevalence of ATTR disease due to a genetic variant depends on the prevalence of specific causative pathologic *TTR* variants that are concentrated in regions of the world, with higher frequencies observed in areas such as County Donegal, Republic of Ireland (1% population prevalence of a pathologic *TTR* genetic variant) or in northern Sweden (4% population prevalence of a pathologic *TTR* variant) (**Table 1**).[6,17-21] ATTR amyloidosis due to a genetic variant is more common in people who are older, and the association of older age with ATTR amyloidosis depends on the genetic variant. Genetic variants are inherited in an autosomal dominant manner. *TTR* is a 4-exon gene residing on chromosome 18 that produces TTR monomers, which form a homotetramer (4 identical subunits of TTR). Most of the 130 gene variants in TTR promote transthyretin protein misfolding and result in ATTR amyloidosis.[22]

Gene variants represent single-nucleotide changes in the *TTR* gene that result in amino acid substitutions, destabilization of TTR, and protein misfolding. The Val30Met variant (V30M or pV50M, causing a substitution of methionine for valine at position 30 of the protein) is the most commonly encountered variant outside of the US and affects approximately 1 in every 500 individuals

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Figure 1. Pathobiology of ATTR Amyloidosis and Cardiac Manifestations



Circulating TTR protein is synthesized by the liver as a homotetramer that dissociates or is proteolytically cleaved into intermediates that misfold and ultimately organize into amyloid fibrils. Amyloid fibrils then deposit in the heart, resulting in arrhythmia, conduction disease often requiring placement, and heart failure.

in the northern regions of Portugal, 4% of individuals in northern Sweden, and approximately 1 in every 1 million people in Japan.[18] People with this genetic variant typically develop ATTR polyneuropathy before age 50 or ATTR cardiomyopathy after age 50. The Thr60Ala variant (T60A or pT80A) originated in the northwest of the Republic of Ireland and causes both cardiomyopathy and polyneuropathy. Overall, ATTR polyneuropathy affects between 5000 and 38 000 people worldwide.[23] The most common *TTR* variant is Val122Ile (V122I or pV142I), which is observed in approximately 3.4% of African American individuals or approximately 1.5 million people in the US. This variant originated in the western coast of Africa and is associated with development of ATTR cardiomyopathy later in life, typically after age 60.[24] There is considerable variation in reported penetrance of Val122Ile, from 7% (based on echocardiography-demonstrated increased wall thickness) to 39% (based on nuclear scintigraphy) to 100% (autopsy specimens).[19-21] These data have led to confusion regarding the prevalence of ATTR cardiomyopathy that results from the Val122Ile variant. However, the presence of this genetic variant is associated with an increased risk for heart failure and mortality, compared with the absence of this genetic variant.[25-27] For both wild-type and variant disease, the mean age at diagnosis is between 74 and 90 years, while women tend to present at approximately 3 years older than men (mean age of 82 vs 78 years for wild-type ATTR, or 77 vs 75 years for variant ATTR from the Val122Ile genotype).[17,28,29]

Pathophysiology

TTR is synthesized by the liver and secreted into the blood. TTR is also synthesized by the choroid plexus in the cerebrospinal fluid and by pigmented retinal epithelium in the vitreous of the eye.[1] Dissociation (or disaggregation into constituent subunits) of the TTR tetramer is the rate-limiting step in amyloid fibril formation and proteolytic cleavage of TTR promotes amyloid formation (**Figure 1**). Aging-associated factors, such as impaired proteostatic homeostasis, including endoplasmic reticulum-associated degradation of misfolded TTR, contribute to development of amyloidosis.[30-32] In patients with ATTR cardiomyopathy, ATTR deposits between cardiac myocytes in the interstitial space, which contribute to impaired diastolic function, progressive ventricular wall thickening, and impaired longitudinal systolic function. Myocellular injury, manifesting as troponin release and abnormal plasma troponin concentration, develops because myocyte damage and necrosis are associated with misfolded protein accumulation and/or microvascular dysfunction.[33] The mechanism underlying predilection of certain organ systems to deposition of TTR amyloid fibrils (termed *organ tropism*) remains poorly understood, but in variant ATTR, shorter amyloid fibril length and other specific aspects of structure are associated with deposition of amyloid in different organs.[34]

Clinical Presentation

ATTR cardiomyopathy develops over years or even decades, often evading clinical diagnosis.[5] Furthermore, ATTR amyloidosis develops in patients who have other common diseases, such as hypertension, that can cause increased LV wall thickness, which may prevent identification of ATTR cardiomyopathy.[35] Deposition of amyloid fibrils in ligamentous structures often precedes deposition in the myocardium by approximately 5 to 15 years.[36] The presence of bilateral carpal tunnel syndrome, spontaneous ligamentous rupture, and/or spinal stenosis in an older patient (>60 years) with heart failure should prompt consideration of ATTR cardiomyopathy.[37] The principal manifestation of ATTR cardiomyopathy is heart failure, typically HFpEF in the early stage of disease, conduction abnormalities such as heart block, and arrhythmia such as atrial fibrillation or ventricular tachycardia (**Table 2**).

Patients with ATTR cardiomyopathy present with symptoms of dyspnea, fatigue, peripheral edema, and palpitations.[6,37] Patients

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with ATTR cardiomyopathy may develop unanticipated hypotension when treated with antihypertensive or standard heart failure medications such as β-blockers or angiotensin receptor/neprilysin inhibitors because of reduced ability to increase LV stroke volume or they may have unexplained and persistent elevations in cardiac-specific biomarkers, such as troponin or natriuretic peptides, due to cardiac injury from amyloid fibrils.[33,38] On echocardiography, patients with ATTR cardiomyopathy typically have increased LV wall thickness, diastolic dysfunction, and an abnormal global longitudinal systolic strain.[37] Patients with ATTR cardiomyopathy also may have increased wall thickness on imaging often without increased electrocardiographic voltage, resulting in an increased ratio of wall thickness or LV mass to electrocardiography voltage.[37]

Assessment and Diagnosis

Biopsy of the affected organ (typically the heart) is the criterion standard for diagnosing ATTR cardiomyopathy and demonstrates amyloid fibril deposits on Congo red staining.[39] Amyloid deposits demonstrate green birefringence under polarized light microscopy.[40] Noncardiac biopsy, such as the abdominal fat aspirate, can be performed, but its sensitivity for diagnosing ATTR amyloidosis is poor. For wild-type ATTR, the sensitivity of abdominal fat aspiration is less than 20%.[41] Identification of amyloid deposits by Congo red staining of cardiac or noncardiac (eg, ligaments, incidental endoscopic, or bone marrow) biopsies should be confirmed by mass spectrometry to define the amyloid precursor protein.[42] Noninvasive imaging with nuclear scintigraphy has largely replaced biopsy for identification of ATTR cardiomyopathy (**Table 3**).

ATTR cardiomyopathy is most commonly diagnosed by combining noninvasive cardiac nuclear imaging to identify amyloid deposits with blood and urine tests to exclude a monoclonal gammopathy process and amyloid light chain (AL) amyloidosis (**Figure 2**).[43] AL amyloidosis is a serious, more rapidly progressive type of amyloid disease that arises from a B-cell neoplasm that overproduces monoclonal κ or λ light chains, which misfold and aggregate as amyloid fibrils. AL amyloidosis typically occurs without multiple myeloma, another B-cell neoplasm, a neoplasm of activated B-cells or plasma cells, but approximately 10% of patients with AL amyloidosis meet criteria for myeloma.[44] Excluding the diagnosis of AL amyloidosis with blood and urine testing is the first step in the noninvasive evaluation of ATTR amyloidosis. To exclude AL amyloidosis, serum free light chain κ:λ ratio and serum and urine plasma electrophoresis with immunofixation should be performed to test for the presence of a monoclonal protein.[44] Serum protein electrophoresis has poor sensitivity (<75%) for identifying the low abundance of monoclonal protein in AL amyloidosis.[6] The sensitivity of serum free light chain ratio and serum and urine immunofixation electrophoresis in AL amyloidosis is approximately 99%.[45] Levels of the serum free light chain ratio can be increased outside the normal reported range because the ratio is increased by kidney dysfunction (impairing kidney clearance of κ light chain), which is more frequently observed in older patients, who are more commonly tested for ATTR amyloidosis. Approximately 10% to 40% of patients with ATTR cardiomyopathy have elevated light chains suggestive of a monoclonal gammopathy of unknown significance (due to a free light chain ratio above the upper limits of normal or abnormal immunofixation result) that does not cause AL amyloidosis and is unrelated to the ATTR process.[6,46]

Table 2. Primary Clinical Manifestations of ATTR Amyloidosis[a]

Organ system	Clinical manifestation
Cardiovascular	• Atrioventricular block • Congestive heart failure • Arrhythmia (atrial fibrillation/flutter, ventricular tachycardia)
Nervous	• Peripheral neuropathy (weakness/numbness in hands and feet) • Autonomic neuropathy (orthostatic hypotension, erectile dysfunction, sweating abnormalities)
Gastrointestinal	Dysmotility (diarrhea, constipation, nausea/vomiting, early satiety)
Musculoskeletal	• Spinal stenosis • Carpal tunnel syndrome • Ligamentous rupture
Kidney	Acute and chronic kidney disease (cardiorenal syndrome, hemodynamically mediated kidney impairment)

[a] Information for this table was adapted from Kittleson et al.[6]

Excluding the diagnosis of AL amyloidosis by blood and urine testing prior to (or concurrent with) imaging is important because the imaging alone cannot distinguish AL and ATTR.[47] Approximately 80% of patients referred for nuclear scintigraphy to diagnose ATTR amyloidosis have normal results for serum free light chain and immunofixation electrophoresis.[48] Nuclear scintigraphy with technetium-labeled, bone-marking radiotracers combined with the absence of a monoclonal protein by blood and urine testing had a positive predictive value of 100% for ATTR cardiomyopathy.[49] The tracers technetium 99m (Tc 99m) pyrophosphate, Tc 99m hydroxymethylene diphosphonate, and Tc 99m-3,3-diphosphono-1, 2-propanodicarboxylic acid can be used in noninvasive ATTR cardiomyopathy identification.[49] After radiotracer injection and a 1- to 3-hour waiting period, imaging is performed using planar and single-photon computed emission tomography to compare uptake of the radiotracer in the myocardium to the bone (rib) structures. If uptake in the myocardium is equal to or greater than uptake in bone, the scan is considered consistent with ATTR amyloidosis. Expert consensus recommendations specify that imaging can be performed 1 to 3 hours after radiotracer injection and must include single-photon computed emission tomography imaging, preferably with computed tomography.[50] Imaging consistent with ATTR cardiomyopathy confirms that the observed pattern of radiotracer signal originates from the myocardium and not the ventricular cavity.[50,51] The absence of tracer signal in the myocardium excludes ATTR cardiomyopathy (with the exception of rare variants, such as Phe64Leu).[52] Direct cardiac biopsy with testing for the precursor protein using Congo red staining followed by mass spectrometry should be considered in patients for whom tracer uptake is not consistent with a specific diagnosis or in patients with a monoclonal gammopathy for whom AL amyloidosis remains a possibility.[42] After ATTR cardiomyopathy is diagnosed, *TTR* genetic testing is necessary to distinguish between hereditary vs wild-type amyloidosis, because the genotype determines available treatment and also provides important information about whether first-degree relatives may have inherited a pathologic variant.[6] Genetic variants that induce TTR misfolding (such as Val122Ile) result in lower circulating prealbumin (typically <20 mg/dL).[20]

Positron emission tomography imaging using amyloid-specific radiotracers may help identify ATTR cardiac amyloidosis

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Table 3. Diagnostic Tests for ATTR Cardiac Amyloidosis

	Echocardiography	Cardiovascular magnetic resonance	Tc 99m scintigraphy	Endomyocardial biopsy	Positron emission tomography
Current role in diagnostic evaluation	• Prognosis • Evaluation of response to therapy	Prognosis	Establish diagnosis	Establish diagnosis	Unclear, under investigation
Principal diagnostic features	• Reduced global longitudinal strain and abnormal regional strain ratios (apical sparing pattern) • Increased wall thickness and increased relative wall thickness • Diastolic dysfunction	• Presence of late gadolinium enhancement • Myocardial signal suppression before blood pool pattern • Increased extracellular volume fraction • Increased native myocardial T1 time	• Semiquantitative uptake grade • SPECT or SPECT/CT required to confirm tracer uptake is myocardial • Heart to contralateral chest ratio (to be used to support interpretation of semiquantitative ratio, and not in isolation) • Heart to whole body ratio	• Presence of Congo red staining • Laser capture tandem mass spectrometry demonstrating TTR protein in amyloid deposits	• Increased myocardial retention index • Increased standardized uptake value ratio • Increased target-to-blood pool ratio
Principal benefits	• Short duration of examination • Can be performed at point of care, nearly universally available • Hemodynamic characterization: no ionizing radiation	• No ionizing radiation • Provides information on function and tissue characterization • Identifies alternative etiologies of cardiomyopathy	• Diagnostic for ATTR-CA in the context of no plasma cell disorder • Widely available	Diagnostic for amyloidosis and type	• Directly images amyloid deposits • Identifies ATTR and non-ATTR amyloid types
Principal limitations	• Image limited by body habitus • Limited information regarding tissue characterization • Diagnostic features are nonspecific and overlap with other cardiomyopathies	• Interpretation and performance of T1 mapping and extracellular volume requires expertise • Image quality limited by patient factors (breathing, tachycardia, technique) • Lack of multicenter study data	• Long tracer incubation period resulting in long examination times (up to 3 h) • Radiation exposure, but minimal • False-positive scans due to blood pool tracer uptake	Invasive technique that carries risk of myocardial perforation/tamponade, arrhythmia, and vascular access complication[39]	Currently investigational use only

Abbreviations: ATTR, amyloidosis from transthyretin; ATTR-CA, variant transthyretin cardiac amyloidosis; SPECT, single-photon emission computed tomography; SPECT/CT, single-photon emission computed tomography with computed tomography attenuation map; Tc 99m, technetium 99m; TTR, transthyretin.

and may be used to monitor response to treatment, but the sensitivity and specificity of this test are unknown.[53] In patients with symptoms of heart failure and echocardiographic findings of unexplained increased myocardial wall thickness and diastolic dysfunction (in the absence of hypertension or other potential etiology), ATTR cardiomyopathy should be considered as a potential diagnosis. Increased wall thickness of 12 mm or greater, LV ejection fraction less than 60%, and relative wall thickness greater than 0.57 mm are echocardiographic features that are associated with ATTR cardiomyopathy in male patients older than 60 years who do not have a history of hypertension.[54] Echocardiography also demonstrates a longitudinal strain pattern in ATTR cardiomyopathy characterized by normal or near-normal longitudinal strain values in the apical LV segments and reduced strain values in the basal LV segments.[55] These strain abnormalities have been observed in other diseases, such as aortic stenosis, and are not specific for ATTR.[56]

Cardiovascular magnetic resonance can directly visualize and quantify the interstitial space expansion caused by amyloid fibril deposition between cardiac myocytes.[57] Following administration of gadolinium contrast, amyloid deposition can be visualized through late gadolinium enhancement imaging. The pattern of late gadolinium enhancement observed is typically diffuse, and regions of subendocardial and transmural enhancement appear distinct from other myocardial processes. Measurement of myocardial T1 time before and after contrast administration can quantify the proportion of the heart tissue occupied by extracellular volume (ECV). ECV is expressed as a percentage and measures the volume of a sample of myocardium that exists as extracellular space that has been increased by amyloid deposition (or interstitial fibrosis). Normal myocardial ECV is typically less than 30% to 32% while ATTR cardiomyopathy is characterized by an increase in ECV that is typically greater than 40%.[50]

Treatment

Treating Heart Failure in Patients With ATTR Cardiomyopathy

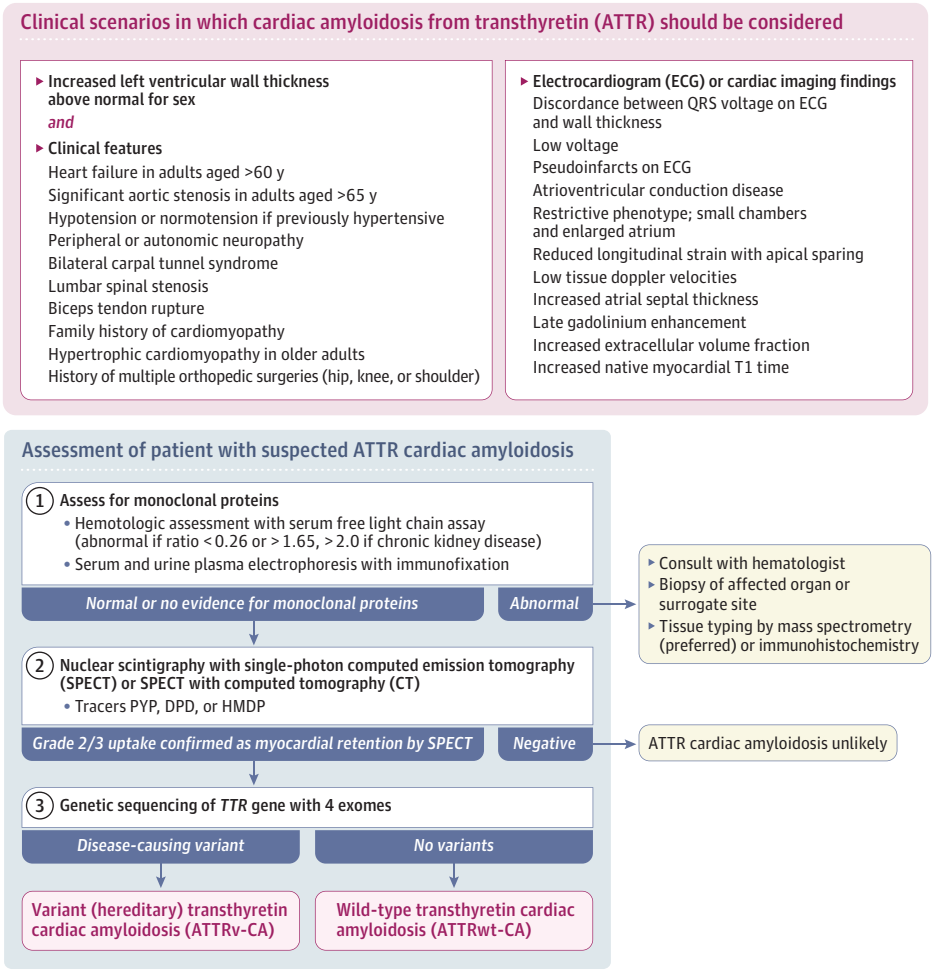
Loop diuretics are the primary treatment for fluid overload and symptomatic relief of patients with ATTR cardiomyopathy and heart failure. Maintenance of euvolemia can be difficult because many patients have low blood pressure due to reduced and fixed stroke volume and low cardiac output, which can be made worse by concurrent autonomic dysfunction in variant ATTR. Patients with ATTR cardiomyopathy may have organ hypoperfusion due to dehydration after diuretic therapy. Acute or chronic kidney disease can also manifest as a cardiorenal syndrome in patients with fluid overload. Because of poor absorption of furosemide in patients with intestinal wall edema, torsemide or bumetanide may be prescribed as alternatives for patients with inadequate response to furosemide. Higher daily doses of loop diuretic, such as greater than 1 mg/kg/d of furosemide equivalent dosing (1 mg of bumetanide = 20 mg of torsemide = 40 mg of furosemide), were associated with worse outcomes.[58]

Mineralocorticoid receptor antagonists (MRAs, including spironolactone and eplerenone) enhance diuresis by loop diuretics and block sodium reabsorption in the distal tubule of nephron to mitigate hypokalemia associated with loop diuretics. In a single-center,

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Figure 2. Noninvasive Diagnosis of ATTR Cardiomyopathy



In the context of clinical, electrocardiographic, or imaging features of ATTR amyloidosis, noninvasive diagnosis can be accomplished using nuclear imaging and evaluation for a plasma cell disorder or monoclonal protein to exclude light chain amyloidosis. Endomyocardial biopsy should be considered in equivocal cases (ie, grade 1 nuclear tracer uptake), inconsistent testing results, or high clinical suspicion for nonamyloid light chain or ATTR amyloid types. Genetic testing is necessary to establish wild-type or variant *TTR* that determined available therapies. DPD indicates 3,3-diphosphono-1,2-propanodicarboxylic acid; HMDP, hydroxymethylene diphosphonate; and PYP, pyrophosphate.

retrospective cohort study of 2371 patients with ATTR cardiomyopathy that used propensity matching, over a median follow-up of 27.8 months (IQR, 10.6-51.3 months), MRAs were independently associated with a reduced risk of mortality (hazard ratio [HR], 0.77 [95% CI, 0.66-0.89]), although overall rates of death were 38% in patients treated with MRAs vs 39.5% in those not treated with MRAs.[59] Among patients with persistent volume overload who do not respond to loop diuretics, the combination of loop and thiazide diuretics can enhance diuresis.

Because of the paucity of randomized clinical trial evidence, expert consensus documents have varying recommendations regarding the role of standard heart failure therapies for patients with ATTR cardiomyopathy.[29,60,61] Antagonists of the renin-angiotensin system, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and angiotensin receptor/neprilysin inhibitors, have not been shown to be associated with reduction in mortality in retrospective cohort studies.[59] Assessment for orthostatic hypotension is important to mitigate the risks associated with neurohormonal antagonists, such as symptomatic hypotension and syncope. While most patients with ATTR cardiomyopathy have a preserved ejection fraction, approximately 20% to 25% have a reduced ejection fraction. Reduced ejection fraction is more common in patients with ATTR cardiomyopathy due to a genetic variant.[59] β-Blockers may prevent the increased heart rate response associated with declines in stroke volume in patients with ATTR cardiomyopathy. Relatively high-dose β-blockers, such as carvedilol, 12.5 to 25 mg, twice daily, when discontinued, were associated with survival improvement.[62] Among 531 patients with ATTR cardiomyopathy and an ejection fraction below 40% in the single-center retrospective cohort study with propensity matching, low-dose β-blockade using bisoprolol, 2.5 mg/d or less, was associated with improved survival (40.8% vs 59.2%; HR, 0.61 [95% CI, 0.45-0.83]), compared with no survival benefit for those with an ejection fraction greater than 40% (33.7% vs 34.8%; HR, 1.00 [95% CI, 0.84-1.2]).[59] While apparently well tolerated in a small, nonrandomized, 3-month observational cohort, no randomized clinical trials are available regarding the safety and efficacy of sodium-glucose cotransporter 2 (SGLT-2) antagonists for ATTR amyloidosis with heart failure.[61,63]

Arrhythmia Treatment in Patients With ATTR Cardiomyopathy

Atrial fibrillation (or atrial flutter) is the most common sustained arrhythmia observed in patients with ATTR cardiomyopathy. Approximately 30% to 70% of patients with ATTR cardiomyopathy have atrial fibrillation at the time of diagnosis.[64-66] Intracardiac thrombi affect approximately 7% to 18% of patients with

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ATTR cardiomyopathy and the development of thrombi appeared unrelated to the CHA_2DS_2-VAS_2C (congestive heart failure, hypertension, age ≥75 years [2 points], diabetes, stroke/transient ischemic attack/thromboembolism [2 points], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65-75 years, sex category [female]) score.[67,68] Anticoagulation for atrial fibrillation is recommended, irrespective of other risk factors for thromboembolic events. Transesophageal echocardiography is useful to exclude left atrial appendage thrombus for all patients with ATTR cardiomyopathy, prior to cardioversion.[69,70] While all patients with ATTR cardiomyopathy and atrial fibrillation should receive anticoagulation, insufficient data exist for recommending anticoagulation with vitamin K antagonists or direct oral anticoagulants because both were associated with similar rates of stroke, transient ischemic attack, or major bleeding.[71] Atrial fibrillation in ATTR cardiomyopathy is not independently associated with increased mortality.[64,65] Therefore, treatment to attain normal sinus rhythm vs rate control should focus on improving symptoms.[65] Permanent pacing is reasonable in patients with ATTR cardiomyopathy and second-degree Mobitz type II atrioventricular block, high-grade atrioventricular block, or third-degree atrioventricular block.[72] Approximately 10% to 40% of patients with ATTR cardiomyopathy require pacemakers.[73] Biventricular pacing (compared with right ventricular pacing) is preferred because it reduces mitral regurgitation severity, preserves New York Heart Association (NYHA) class, and preserves ejection fraction in observational cohort data.[74] Nonsustained ventricular arrhythmias commonly affect more than 60% of patients with ATTR cardiomyopathy who undergo monitoring for arrhythmias; however, their prognostic significance is unclear. Sudden cardiac death occurs in approximately 2% to 5% of patients with ATTR cardiomyopathy and current Heart Rhythm Society guidelines do not recommend routine placement of implantable cardioverter-defibrillator for primary prevention.[75] However, if a permanent pacemaker is placed for atrioventricular block that meets guideline recommendations, including second-degree Mobitz type II atrioventricular block, high-grade atrioventricular block, or third-degree atrioventricular block, placing an implantable cardioverter defibrillator is reasonable if the patient has an anticipated survival of greater than 1 year.[72]

Treatment With Disease-Modifying Therapies

Treatment of ATTR cardiomyopathy includes medications that bind to and kinetically stabilize the TTR protein to inhibit tetramer dissociation, thereby slowing amyloid formation (tafamidis, acoramidis, and diflunisal), and agents that suppress hepatic TTR protein synthesis with small interfering mRNAs (patisiran, vutrisiran) or antisense oligonucleotides (inotersen, eplontersen) (**Table 4**).[76-84] Therapies that suppress hepatic synthesis of TTR (patisiran, vutrisiran, inotersen, and eplontersen) were evaluated in clinical trials for patients with ATTR polyneuropathy resulting in regulatory approval for patients with ATTR polyneuropathy (with or without cardiomyopathy; Table 4).[78-82,85,86] Subsequently, certain of these therapies have been evaluated in those with ATTR cardiomyopathy specifically, but none of these agents are currently approved for ATTR cardiomyopathy without polyneuropathy.[87,88] Another promising strategy is amyloid depletion or removal of deposits with antibody-driven phagocytic degradation.[89]

Therapies That Stabilize the TTR Protein

Tafamidis is the only currently approved therapy for patients with ATTR cardiomyopathy due to either wild-type or variant disease. In a clinical trial of 441 participants with ATTR cardiomyopathy randomized to receive either 20 or 80 mg of tafamidis daily or placebo for 30 months, tafamidis reduced mortality (42.9% vs 29.5%) with a number needed to treat of 7 to 8 participants to prevent 1 death over 30 months and reduced cardiovascular and all-cause hospitalizations from 0.7/year to 0.48/year with a number needed to treat of 4 to prevent 1 cardiovascular hospitalization over a year.[76] Efficacy was greater in participants with earlier-stage disease (NYHA class I to II). Patients with class III heart failure who received tafamidis had a higher rate of cardiovascular hospitalizations than those randomized to placebo; however, longer-term (58.5-month) data in the open-label extension of this trial demonstrated a survival advantage for those even with NYHA class III symptoms at baseline.[90] Additionally, at 30 months, tafamidis slowed the decline in functional capacity (57-m decline with tafamidis vs 133-m decline with placebo in the 6-minute walk test) and quality of life (7-point decline with tafamidis vs 21-point decline with placebo in the Kansas City Cardiomyopathy Questionnaire overall score; score range, 0-100, with 100 indicating best).[76] Adverse effects, such as diarrhea and constipation, were typically mild to moderate in severity and were less common with tafamidis than placebo. Permanent discontinuation of tafamidis or placebo because of adverse events was less common in the tafamidis groups than in the placebo group (0.8% vs 2.3%).[76]

Diflunisal is an approved nonsteroidal anti-inflammatory drug that stabilizes TTR protein and can be administered to selected patients who have ATTR cardiomyopathy without advanced kidney disease who cannot receive tafamidis. Kidney function must be carefully monitored in patients taking diflunisal. Small (100- to 150-patient), nonrandomized, single-center studies of diflunisal-treated patients with ATTR cardiomyopathy vs untreated patients demonstrated improvement in left atrial volume index (+4.6 mL/m^2 for untreated patients vs −1.4 mL/m^2 for treated patients, $P = .002$), cardiac troponin I (+0.03 ng/mL for untreated patients vs −0.01 ng/mL for treated patients), and global longitudinal strain (+1.2% for untreated patients vs +0.1% for treated patients) after 1 year of treatment.[84,91] Survival in nonrandomized cohort studies at 3 years was 79% for tafamidis compared with 77% for people who received diflunisal and 27% in those not taking stablizers.[92]

Acoramidis, a drug that stabilizes TTR protein, was studied in the ATTRibute-CM randomized trial, in which 632 patients with ATTR cardiomyopathy were randomized (2:1) to acoramidis (800 mg twice a day) or placebo for 30 months. Compared with placebo, acoramidis was associated with an absolute reduction in mortality of 6.4% (25% relative risk reduction) and statistically significant reduction in the frequency of cardiovascular hospitalizations from 0.45 to 0.22 per year.[77] The incidence of serious adverse events was lower in the acoramidis than in the placebo groups (54.6% vs 64.9%).

Therapies That Suppress TTR Protein Expression

Patisiran, an approved drug for variant ATTR polyneuropathy that reduces hepatic synthesis of TTR and circulating levels of TTR, was evaluated in the APOLLO-B trial of 360 patients with ATTR

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Table 4. Therapies for ATTR Amyloidosis

	Therapy							
	Tafamidis	Acoramidis	Diflunisal	Patisiran	Inotersen	Vutrisiran	Eplontersen
Regulatory approval	Variant and wild-type ATTR cardiomyopathy and polyneuropathy	Pending (2023)	Approved NSAID, off-label utilization in ATTR polyneuropathy and cardiomyopathy	Variant ATTR polyneuropathy	Variant ATTR polyneuropathy	Variant ATTR polyneuropathy	Variant ATTR polyneuropathy
Class and mechanism of action	Benzoxazole derivative that binds with high affinity and selectivity to TTR and kinetically stabilizes the tetramer, slowing monomer formation, misfolding, and amyloidogenesis	3-(3-[3,5-Dimethyl-1H-pyrazol-4-yl]propoxy)-4-fluorobenzoic acid, which stabilizes TTR tetramer by forming H-bonds with S117 to mimic the protective effect of *TTR* variant T119M	NSAID that complexes to the thyroxine binding site and kinetically stabilizes circulating TTR tetramers, inhibiting release of the TTR monomer required for amyloidogenesis	siRNA binds proteins that form the RISC, with release of passenger strand and antisense strand bound to RISC binds to target TTR mRNA, which is then cleaved by Argonaute2	ASOs bind target TTR mRNA, forming a DNA/RNA heteroduplex that binds to and activates RNase H1, which then cleaves the TTR mRNA	siRNA binds proteins that form the RISC, with release of passenger strand and antisense strand bound to RISC binds to target TTR mRNA, which is then cleaved by Argonaute2	ASOs bind target TTR mRNA, forming a DNA/RNA heteroduplex that binds to and activates RNase H1, which then cleaves the TTR mRNA
Dose and frequency	61 mg orally daily of tafamidis free salt; 80 mg daily of tafamidis meglumine; 20 mg daily of tafamidis meglumine	800 mg orally twice daily	250 mg orally twice daily	0.3 mg/kg (up to a maximal dose of 30 mg) IV every 3 wk	284 mg subcutaneously weekly	25 mg subcutaneously every 3 mo	45 mg subcutaneously every 4 wk
Formulation	Tablet	Tablet	Tablet	Lipid nanoparticle	None	GalNAc-conjugated siRNA	GalNAc-conjugated ASO
Additional medication required during treatment	None	None	None	Premedication: IV corticosteroid (dexamethasone, 10 mg, or equivalent) Oral acetaminophen IV or oral H1 blocker IV or oral H2 blocker During treatment: Vitamin A supplementation daily	During treatment: vitamin A supplementation daily	During treatment: vitamin A supplementation daily	During treatment: vitamin A supplementation daily

(*continued*)

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Table 4. Therapies for ATTR Amyloidosis (continued)

	Therapy						
	Tafamidis	Acoramidis	Diflunisal	Patisiran	Inotersen	Vutrisiran	Eplontersen
Results of testing in clinical trial(s)	ATTR-ACT, a multicenter, international, double-blind, placebo-controlled, phase 3 trial in 441 patients with ATTR cardiomyopathy comparing tafamidis, 20 or 80 mg, with placebo, randomized 1:2:2 respectively, for 30 mo[76]	ATTRibute-CM, an international, multicenter, double-blind, placebo-controlled phase 3 trial in 632 patients with ATTR cardiomyopathy were randomized (2:1) to acoramidis or placebo for 30 mo[77]	Diflunisal Trial, an international randomized, double-blind, placebo-controlled study conducted among 130 patients with symptomatic variant ATTR polyneuropathy comparing diflunisal, 250 mg, orally twice daily vs placebo for 2 y[78]	APOLLO trial, an international randomized, double-blind, placebo-controlled study conducted among 225 patients with symptomatic variant ATTR polyneuropathy comparing IV patisiran (0.3 mg/kg) or IV placebo every 3 wk in a 2:1 randomization[79] APOLLO-B trial, an international randomized, double-blind, placebo-controlled study conducted in 360 patients with symptomatic ATTR-CC comparing IV patisiran (0.3 mg/kg) or IV placebo every 3 wk in a 1:1 randomization	Neuro-TTR trial, an international, randomized, double-blind, placebo-controlled, 15-mo phase 3 trial in 172 patients with variant ATTR polyneuropathy (112 in the inotersen and 60 in the placebo group) with stage 1 (patient is ambulatory) or stage 2 (patient is ambulatory with assistance) amyloidosis, randomly assigned, in a 2:1 ratio, to receive weekly subcutaneous injections of inotersen (300 mg) or placebo[80]	HELIOS-A, a phase 3, global, open-label study comparing the efficacy and safety of vutrisiran (n = 122) with a patisiran reference group (n = 42) and an external placebo group (APOLLO study, n = 77) in which patients with variant ATTR polyneuropathy were randomized 3:1 to subcutaneous vutrisiran, 25 mg, every 3 mo or IV patisiran, 0.3 mg/kg, every 3 wk for 18 mo[81]	NEURO-TTRansform, an open-label, single-group, phase 3 trial in 168 adults with stage 1 or 2 variant ATTR polyneuropathy treated with subcutaneous eplontersen (45 mg every 4 wk; n = 144); a small reference group received subcutaneous inotersen (300 mg weekly; n = 24) and subcutaneous placebo weekly (in NEURO-TTR [n = 60])[82]
Efficacy	In ATTR cardiomyopathy, reduced all-cause mortality by 13% (absolute) and cardiovascular-related hospitalizations by 32% (relative risk reduction) and reduced the decline in functional capacity (75.7-m difference in 6-min walk test) and QOL (13.7-point difference in the Kansas City Cardiomyopathy Questionnaire) after 30 mo. In ATTR polyneuropathy, tafamidis, 20 mg, was associated with a significant reduction in worsening of most neurologic measures including the Neuropathy Impairment Score in the Lower Limbs score. Tafamidis is approved by the EMA and not FDA for ATTR polyneuropathy	The primary end point, a 4-step hierarchy including all-cause mortality, cardiovascular hospitalizations, NT-proBNP, and 6-min walk test distance demonstrated a win ratio of 1.8 (95% CI, 1.4-2.2; $P < .001$). All-cause mortality and cardiovascular hospitalizations contributed 58% of the win ratio result. An absolute mortality reduction of 6.4% (relative risk reduction of 25%, not significant) was observed with acoramidis vs placebo and the frequency of cardiovascular hospitalizations was reduced by 50%	In ATTR polyneuropathy, reduced the rate of progression of neurologic impairment with a difference in the NIS+7 nerve test score of 16.3 points and preserved QOL with a difference in SF-36 physical component score of 6.1 points over 2 y. In nonrandomized trials, cohort studies of ATTR cardiomyopathy, diflunisal was associated with a decrease in mortality (23% vs 73% at 3 y), left atrial volume index (+4.6 vs −1.4 mL/m^2), cardiac troponin I (+0.03 vs −0.01 ng/mL), and global longitudinal strain (+1.2% for untreated vs +0.1% for treated patients)	In ATTR polyneuropathy, reduced the progression of neurologic impairment with a mean difference of −34.0 points in NIS+7, preserved QOL with a mean difference of 21.1 points in the Norfolk QOL-DN, gait speed (difference of 0.3 m/s), and nutritional status (difference of 116 in the modified BMI). In ATTR cardiomyopathy (APOLLO-B), preserved functional capacity (14.7-m difference in 6-min hall walk test), health status, QOL (3.7-point difference in the Kansas City Cardiomyopathy Questionnaire), and cardiac function (−9.45-g difference in left ventricular mass and 3.00-mL difference in stroke volume). The FDA declined to approve patisiran for ATTR cardiomyopathy	In ATTR polyneuropathy, reduced the progression of neurologic impairment (19.7-point difference in modified NIS+7) and preserved QOL (11.7-point difference in Norfolk QOL-DN score) compared with placebo	In ATTR polyneuropathy, reduced the progression of neurologic impairment (modified NIS+7 difference of 17 points), preserved QOL (16.2-point difference in Norfolk QOL-DN score) at 9 mo and gait speed (0.24 m/s difference), nutritional status (modified BMI difference of 140.7), and overall disability (Rasch-built Overall Disability Scale; difference of 8.4 points) at 18 mo	In ATTR polyneuropathy, met the co-primary end point of change from baseline in the modified NIS+7 (mean difference of −24.8 points) and the Norfolk QoL-DN (mean difference, 19.7 points) at wk 66

(*continued*)

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Table 4. Therapies for ATTR Amyloidosis (continued)

	Therapy						
	Tafamidis	Acoramidis	Diflunisal	Patisiran	Inotersen	Vutrisiran	Eplontersen
Contraindications	None	None	Patients with history of gastrointestinal bleeding, significant CKD (eg, eGFR <40 mL/min/1.73 m^2), with high-dose loop diuretics or with oral anticoagulants	None	Platelet count, <100 × 10^3/μL. Urine protein to creatinine ratio >1000 mg/g	None	None
Adverse effects	None	None	NSAIDs can increase risk of cardiovascular thrombotic events, cause gastrointestinal bleeding or CKD	Infusion-related reactions (19%) and 5% led to infusion interruption, <1% resulted in permanent discontinuation	Can cause thrombocytopenia, severe and sudden in 3% and glomerulonephritis in 3%, which needs to be monitored according to REMS procedure	Arthralgias (11%)	Unknown
Current cost	$239 000/y	Not known	$755/y	$450 000/y	$390 000/y	$572 884/y	$525 564/y
Duration	Lifelong	Lifelong	Lifelong	Lifelong	Lifelong	Lifelong	Lifelong
Comment	Cost-effectiveness analysis demonstrates that price reduction of 92% is required to meet the cost-effectiveness threshold of $100 000/quality-adjusted life-year. Efficacy is better with earlier initiation of therapy before significant cardiac dysfunction has ensued	Not yet approved for use (2023)	Off-label administration. Safety and long-term efficacy not established. Concern about NSAID use in patients with CVD including those taking anticoagulation. The low dose could ameliorate concerns regarding adverse effects. Used in carriers of TTR variants to prevent or forestall development of disease	Tested in ATTR cardiomyopathy but not FDA approved	Likely to be discontinued given adverse effects and approval of eplontersen for variant ATTR polyneuropathy	Being evaluated in ATTR cardiomyopathy in the HELIOS-B trial	Being evaluated in ATTR cardiomyopathy in the CARDIO-TTRansform Trial

Abbreviations: ASOs, antisense oligonucleotides; ATTR, amyloidosis from transthyretin; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; FDA, Food and Drug Administration; GalNAc, N-acetylgalactosamine; IV, intravenous; NIS+7, Neuropathy Impairment Score plus 7; NSAID, nonsteroidal anti-inflammatory drug; NT-proBNP, N-terminal pro-brain natriuretic peptide; QOL, quality of life; QOL-DN, Quality of Life–Diabetic Neuropathy; REMS, risk evaluation and mitigation strategies; RISC, RNA-induced silencing complex; RNase H1, ribonuclease H1; SF-36, 36-Item Short-Form Health Survey; siRNA, small interfering RNA; TTR, transthyretin.

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Table 5. Staging Systems for ATTR Cardiac Amyloidosis

Staging system	Staging criteria	Median survival[a]		
		Stage 1	Stage 2	Stage 3
Scoring		0 Criteria for Mayo or NAC, score 1 to 3 for Columbia	1 Criterion for Mayo or NAC, score 4 to 6 for Columbia	2 Criteria for Mayo or NAC, score 7 to 9 for Columbia
Mayo Clinic (wild-type ATTR)[33]	Troponin *t* >0.05 ng/mL NT-proBNP >3000 pg/mL	66 mo	40 mo	20 mo
National Amyloidosis Centre (NAC) (wild-type and variant ATTR)[38]	eGFR <45 mL/min/1.73 m2 NT-proBNP >3000 pg/mL	69 mo	47 mo	24 mo
Columbia University (wild-type and variant ATTR)[58]	Mayo or NAC score (0 to 2 points) Daily dose of furosemide equivalents: 0 mg/kg (0 points), >0-0.5 mg/kg (1 point), >0.5-1 mg/kg (2 points), and >1 mg/kg (3 points) NYHA class I-IV (1 to 4 points)	91 mo	36 mo (Mayo) and 39 mo (NAC)	20 mo

Abbreviations: ATTR, amyloidosis from transthyretin; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

[a] The Columbia University score ranges from 1 to 9.

cardiomyopathy. Patisiran significantly improved 6-minute walk distance by 14.7 m, compared with control, and improved the Kansas City Cardiomyopathy Questionnaire overall score by 3.7 points (score range, 0 to 100, with higher scores indicating better health) compared with placebo. Adverse events occurred in 91% of patients in the patisiran group and 94% of patients in the placebo group. The most common adverse effects associated with patisiran occurred in relation to the infusion and consisted of arthralgia (8% vs 4%) and muscle spasms (7% vs 2%).[88] Patisiran was not approved by the US Food and Drug Administration for ATTR cardiomyopathy but remains available for variant ATTR polyneuropathy (that may include concurrent cardiomyopathy). As with all agents that suppress hepatic TTR protein synthesis, vitamin A supplementation (at the recommended daily allowance of 2500 IU) is recommended with patisiran administration to prevent clinical manifestations of vitamin A deficiency due to impaired vitamin A transport that may occur with reduced circulating TTR.

Prognosis

Prealbumin may be a useful marker to assess treatment efficacy. Compared with baseline, increased prealbumin concentration of a median of 7.5 mg/dL is observed with stabilizer drug therapy (mean increases from baseline of 50% with tafamidis-free salt and 53% with acoramidis) and on average a more than 80% reduction in prealbumin is observed following TTR-suppressing drug therapy (such as patisiran, vutrisiran, and eplontersen).[83,93,94] There are established staging systems for ATTR cardiomyopathy that incorporate cardiac biomarkers including troponin and natriuretic peptide levels (Mayo), estimated glomerular filtration rate and natriuretic peptides (National Amyloidosis Centre), or biomarker plus NYHA class and daily dose of loop diuretics expressed in furosemide equivalents in milligrams per kilogram (Columbia University) (**Table 5**).[33,38,58] Survival appears worse in ATTR cardiomyopathy with the Val122Ile variant as compared with wild-type ATTR cardiomyopathy, perhaps attributable to biology, comorbidities, or inadequate access to appropriate care.[38,95]

Limitations

This review has several limitations. First, some evidence was based on relatively small studies or retrospective studies that were likely influenced by selection and referral bias. Second, the quality of included evidence was not formally evaluated. Third, some relevant studies may have been missed.

Conclusions

ATTR amyloidosis causes cardiomyopathy in up to 150 000 people in the US. Tafamidis is the only currently approved therapy that slowed production of ATTR amyloidosis and improved survival and prevented hospitalization, compared with placebo, in people with ATTR-associated cardiomyopathy.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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