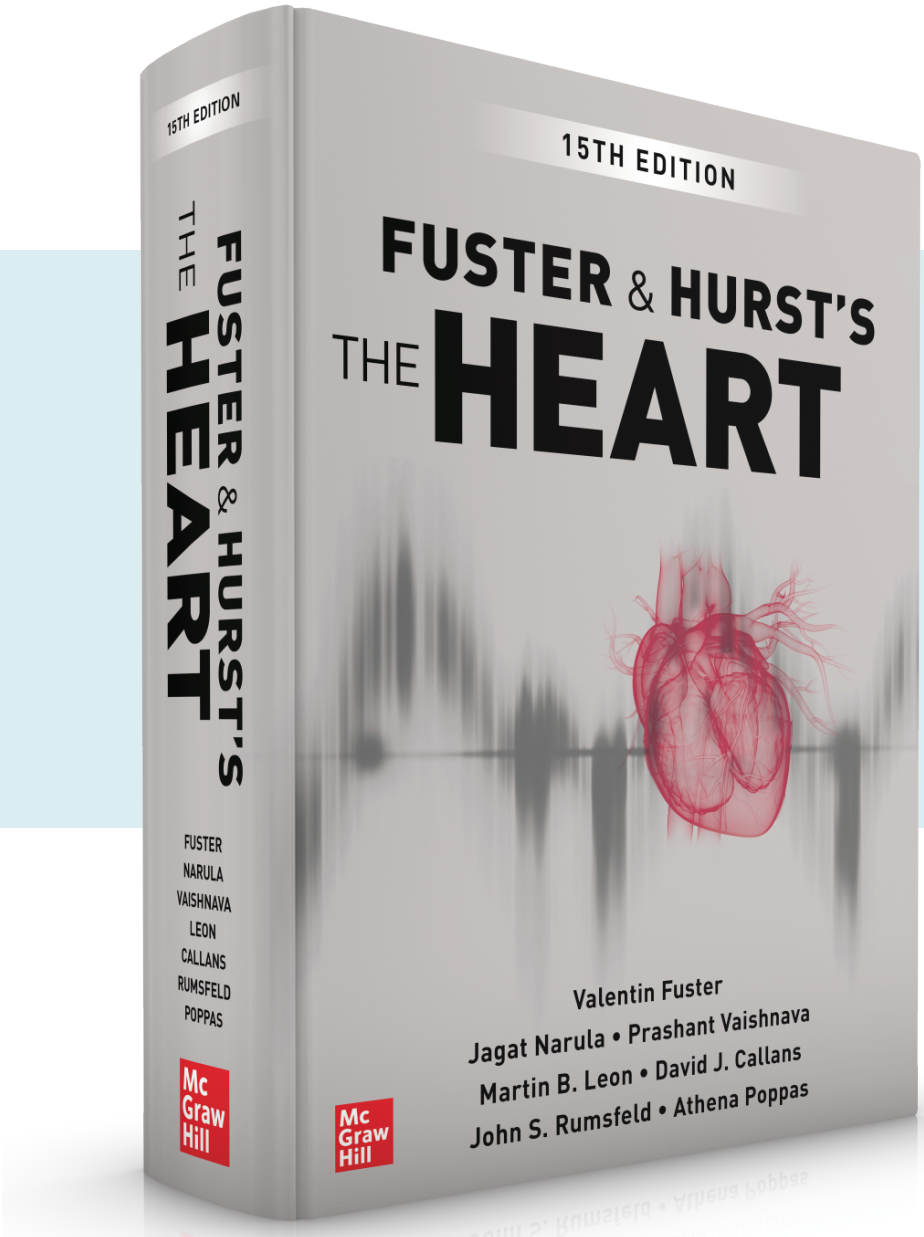
Mc Graw Hill

FUSTER & HURST'S THE HEART 15TH EDITION

Sample Chapter

**CHAPTER 43:**
Cardiac Amyloidosis




BUY NOW

Because learning changes everything.®

mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.

Mc Graw Hill

FUSTER & HURST'S THE HEART 15TH EDITION

43

# Cardiac Amyloidosis

Morie A. Gertz, Jagat Narula, Edgar Argulian, and Sumeet S. Mitter

## CHAPTER OUTLINE



BUY NOW

Because learning changes everything.®

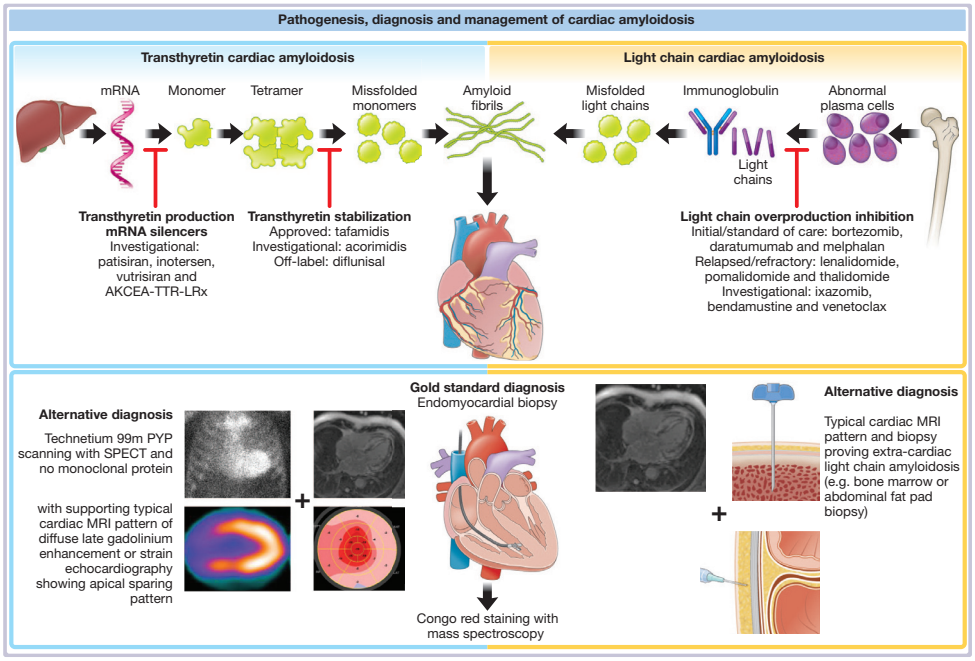
mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.

Mc Graw Hill

FUSTER & HURST'S THE HEART 15TH EDITION






**Chapter 43 Fuster and Hurst's Central Illustration.** Cardiac amyloidosis leads to left ventricular wall thickening and primarily presents with heart failure with preserved ejection fraction (HFpEF) in early stages of the disease. Pathogenesis and the mechanisms of action of approved, investigational, and off-label therapies for transthyretin cardiac amyloidosis and light chain cardiac amyloidosis are shown in the upper panel. Gold standard and alternative methods of diagnosis are depicted in the lower panel.

## CHAPTER SUMMARY

This chapter discusses prevalence, pathophysiology, contemporary invasive and noninvasive diagnosis, and emerging management strategies for cardiac amyloidosis, including both wildtype and variant transthyretin disease as well as light-chain disease (see Fuster and Hurst's Central Illustration). Novel therapies can alter the natural history of cardiac amyloidosis and thus the condition should be considered as a differential diagnosis in any individual with heart failure with preserved ejection fraction, increased left ventricular wall thickness beyond 1.2 cm, and other concerning comorbid conditions including but not limited to atrial fibrillation, carpal tunnel syndrome, and autonomic dysfunction. In variant transthyretin amyloidosis, particularly the V142I pathogenic variant affecting 3% to 4% of Black Americans, facilitating genetic cascade testing in first-degree family members, and subsequent earlier recognition of phenotypic disease and treatment with transthyretin stabilizers, may result in slower disease progression and greater mortality benefit. Ongoing clinical trials using transthyretin silencers may dramatically alter the field if they also show morality benefit and less disease progression for both wildtype and/or variant disease. Additionally, if left untreated, light-chain cardiac amyloidosis is a very fatal disease; however, achieving hematologic response in patients with the condition, either with chemotherapy with bortezomib-based regimens or the anti-CD-38 monoclonal antibody daratumumab, can substantially alter prognosis.

BUY NOW

Because learning changes everything.®

mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.

Mc Graw Hill



## HISTORY

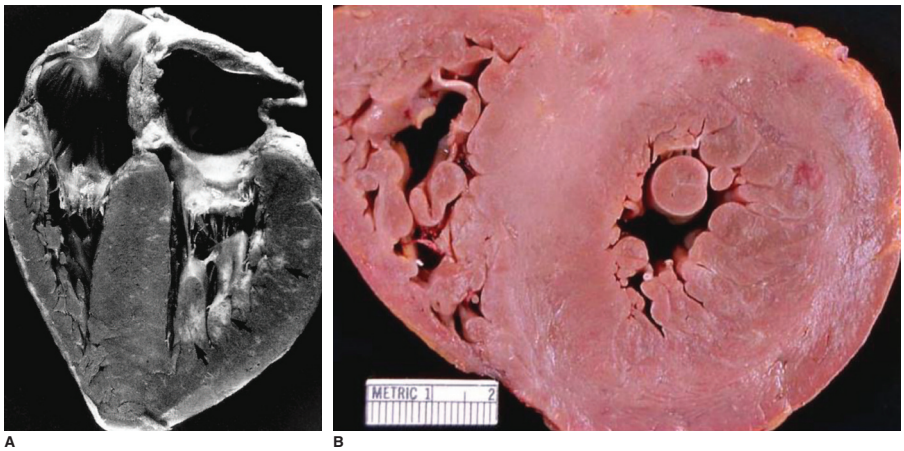
Rudolf Virchow described the reaction of amyloid deposits with iodine and sulfuric acid in 1853. Because this reaction was positive, he assumed that these deposits were starch-like and coined the term *amyloid* (derived from *amylum*, the Latin word for "starch")[1] (**Fig. 43–1**). However, they were later found to be devoid of cellulose by Carl Freidreich and in fact were more albuminoid.[2] In ensuing decades after the introduction of Congo red staining, they were found to have apple-green birefringence under polarized light with a beta pleat structure composing the amyloid fibers.

## PATHOPHYSIOLOGY

Today, amyloidosis reflects a localized or systemic process as a result of at least 30 precursor proteins that destabilize, rearranging into such beta-pleated sheets that make up the fibers that can deposit in various organs. Amyloid deposits are all extracellular and appear hyaline-like and amorphous when stained with hematoxylin and eosin (**Fig. 43–2**). As mentioned, under polarized light, amyloid deposits exhibit apple-green birefringence with Congo red staining (Fig. 43–2). This finding in any tissue is the gold standard for diagnosis of amyloidosis. Alternatively, some pathology labs will perform staining with sodium sulphate-Alcian Blue in preference to Congo red.

Cardiac amyloidosis is most often due to misfolded amyloid light-chain (AL) disease and amyloid transthyretin (ATTR) aggregates (**Table 43–1**) that lead to a restrictive cardiomyopathy from amyloid infiltration into the extracellular space of the myocardium.[3] In the former case, AL disease is the result of a monoclonal plasma cell producing immunoglobulins, from which the light chain breaks off and rearranges to form amyloid deposits. The heart is affected in 50% to 75% of AL disease cases. ATTR disease arises from the breakdown of the tetramer transthyretin protein (or pre-albumin) made primarily in the liver into monomers that destabilize and rearrange into amyloid fibers. Transthyretin functions to transport <5% of the thyroxine as well as retinol-binding protein. Transthyretin is also made in small amounts in the choroid plexus for the cerebrospinal fluid and the retinal pigmented cells for the vitreous of the eye. The encoding gene for transthyretin lies within chromosome 18. A pathologic state can be the result of wild-type ATTR (wtATTR) (formerly senile or age-related ATTR disease) disease that primarily affects the heart or variant ATTR (vATTR) due to more than 130 mutations that lead to varying degrees cardiomyopathy and neuropathy (**Fig. 43–3**). The most common mutation in the United States is Val122Ile (p.V142I), implying valine is substituted by isoleucine at amino acid sequence 122 in the gene and is found in 3.4% of Black American population.[4] The mutation is also common among individuals of African Caribbean descent. Untreated median survival of AL, vATTR, and wtATTR cardiomyopathy is 1.5 years, 2.5 years, and 3.6 years, respectively.[5] Thankfully the natural history of these disease states is rapidly changing with earlier detection and the advent of novel therapies. Rarer forms of cardiac amyloidosis are caused by amyloid acquired (AA) due to rheumatologic or chronic inflammatory/infectious processes, ApoA4 due to apolipoprotein 4, and isolated atrial amyloidosis (IAA) from an overproduction of atrial natriuretic peptide leading to primarily atrial amyloid manifesting often with atrial fibrillation[3,6] (Table 43–1).

Cardiac amyloidosis leads to left ventricular wall thickening and primarily presents with heart failure with preserved ejection fraction (HFpEF) in early stages of the disease. It is often confused with hypertensive heart disease or hypertrophic cardiomyopathy on echocardiography. When recognized late,




A B

**Figure 43–1.** **(A)** and **(B)**Cardiac amyloid, note the marked thickening of the right and left ventricular walls. The white deposits of amyloid resulted in the incorrect labeling as "lardaceous degeneration" by Rokitansky in 1842 as "resembling bacon".

BUY NOW

Because learning changes everything.®

mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.

Mc Graw Hill

FUSTER & HURST'S THE HEART 15TH EDITION



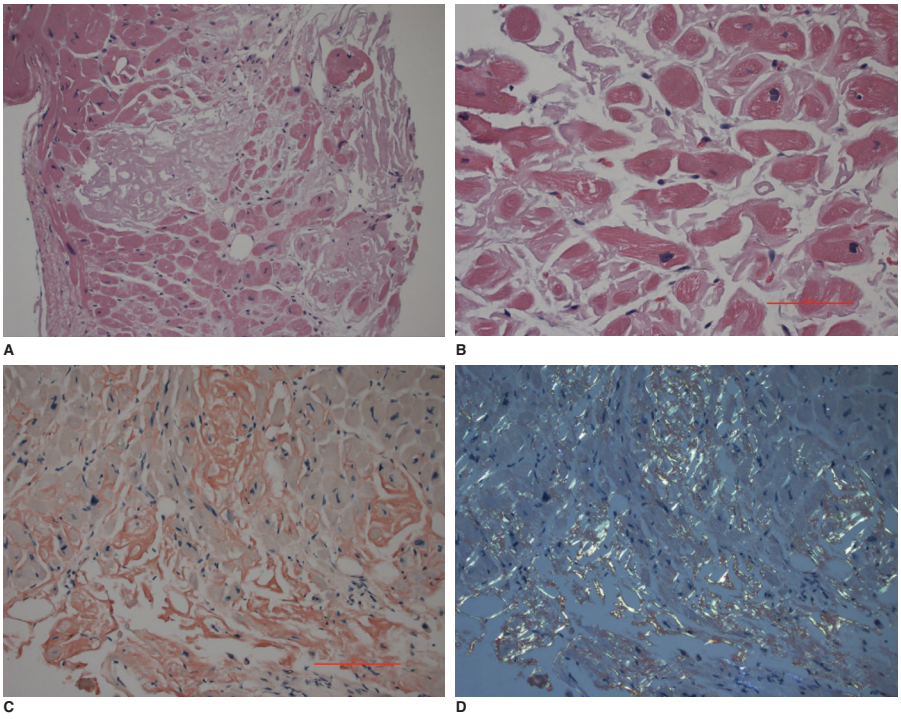



**Figure 43–2.** Endomyocardial biopsy demonstrating interstitial deposits of amyloid on hematoxylin and eosin staining at **(A)** 200x magnification and **(B)** 400x magnification as well as with Congo red staining at **(C)** 400x magnification and **(D)** under polarized light at 400x magnification showing characteristic apple-green birefringence.

**TABLE 43–1. Types of Cardiac Amyloidosis**

| Precursor Protein | Age of Onset | Other Disease Manifestations | Current Therapies |
|---|---|---|---|
| Light Chain | 50 and above | Renal disease, Autonomic dysfunction, Carpal tunnel disease, Pleural effusions, Periorbital purpura | Chemotherapy targeting clonal plasma cell including proteosome inhibitor, daratumumab |
| Wild-Type Transthyretin | 70 and above | Spinal stenosis, Aortic stenosis, Carpal tunnel disease | Tafamidis<br>Acorimidis (in Phase 3 testing)<br>Diflunisal (off label) |
| Variant Transthyretin | 20-70 (varies with pathogenic mutation) | Length-dependent poly sensorimotor neuropathy, Autonomic dysfunction, Carpal tunnel disease | Patisiran and inotersen if concomitant variant ATTR neuropathy |
| Acquired | Adolescent and above | Liver, kidney (heart rare) | Treat underlying cause |
| Apolipoprotein A4 | Unknown | Unknown | Unknown |
| Isolated Atrial | Unknown | Atrial fibrillation | None |

BUY NOW

Because learning changes everything.®

mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.

Mc Graw Hill

FUSTER & HURST'S THE HEART 15TH EDITION



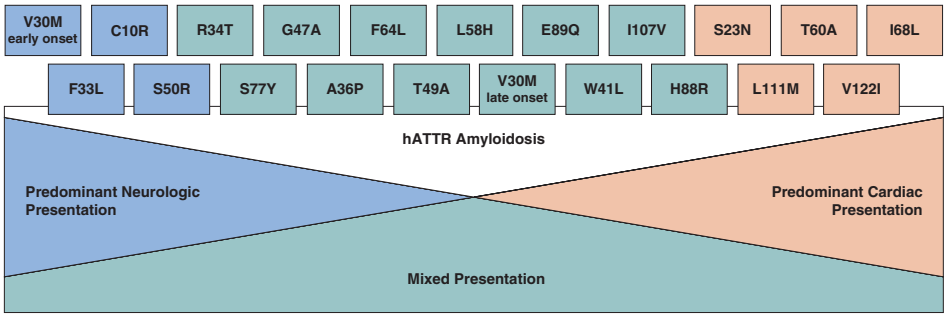



**Figure 43–3.** Demonstration of cardiac and neurologic phenotypes based on specific vTTR pathogenic mutations.

left ventricular dysfunction may be present and portends to a worse prognosis.

## PREVALENCE

The true prevalence of cardiac amyloidosis is not known. Immunoglobulin light-chain amyloidosis has an incidence of 10 patients per million per year, with no evidence of increased frequency over the last 30 years (based on figures from the US, Great Britain, and Europe).[7] Hereditary ATTR prevalence is estimated to be 1 in 100,000 persons in the United States; worldwide prevalence is estimated to be 50,000 persons. Mixed phenotypes with both polyneuropathy and cardiomyopathy can occur in 60% of patients.[8] Wild-type ATTR amyloidosis has an unknown prevalence but can be seen in as many as 25% of autopsies in patients over the age of 80.[9] Today, HFpEF accounts for 50% of hospitalized heart failure.[10] In one recent study of hospitalized HFpEF patients undergoing endomyocardial biopsy to further phenotype disease, 14% had cardiac amyloidosis (including AL, ATTR, and AA disease).[11] Labeling cardiac amyloidosis as a rare disease may actually be a misnomer.

## LIGHT-CHAIN AMYLOIDOSIS

Immunoglobulin light-chain amyloidosis represents a clonal plasma cell disorder with an estimated 3500 to 5000 new patients diagnosed annually in the United States. Although this can occur from the misfolding of kappa or lambda immunoglobulin light chains, over 70% of cardiac amyloidosis is lambda-associated, suggesting a unique predisposition for lambda light chains to deposit in the heart when compared to kappa light chains.[12] Occasionally, heavy chains can be found by mass spectroscopic analysis. Progressive build-up of the light-chain amyloid fibers leads to restrictive myopathy and hence a heart failure syndrome due to an elevation in left ventricular filling pressures in the setting of a small left ventricular cavity. Electrical dysfunction with atrial fibrillation and atrial standstill are well reported.

Presentation can be nonspecific and varied and in addition to HFpEF can include nephrotic range proteinuria, carpal tunnel syndrome, periorbital purpura, macroglossia, diarrhea, and autonomic dysfunction. Initial assessment for AL cardiomyopathy when assessing a patient with HFpEF in the absence of hypertension should include serum immunoglobulin-free light-chain assay and serum and urine immunofixation studies. Serum and urine electrophoresis lack significant sensitivity to rule out AL disease and should not be ordered. Should serum and urine markers raise concern for AL disease, a referral to an oncologist should be made at which point fat pad and/or bone marrow biopsy can be performed to obtain tissue needed for diagnostic confirmation. Plasmacytoma with a plasma cell population occupying <20% of the bone marrow is consistent with isolated AL disease, while higher concentrations of plasma cells would indicate multiple myeloma with AL features. The plasma cells in the bone marrow are genetically abnormal, with 50% showing translocations between chromosome 11 and chromosome 14.[12] Occasionally, immunoglobulin light-chain amyloidosis can be seen from nonplasma cell disorders, such as chronic lymphatic leukemia, Waldenström macroglobulinemia, and marginal zone lymphoma.[14] If such biopsy specimens do not detect amyloid, endomyocardial biopsy should be obtained if multimodality imaging raises the index of suspicion for cardiac amyloidosis.

## WILD-TYPE TRANSTHYRETIN AMYLOIDOSIS

For unclear reasons in some older individuals, the native tetramer conformation of the TTR protein dissociates into monomers that can misfold into beta sheet–rich fibers that deposit mainly in the heart, but also can lead to biceps tendon rupture and lumbar stenosis.[15,16] Carpal tunnel syndrome is also common and should raise concern for cardiac amyloidosis if elicited in the history of any patient with HFpEF. While peripheral and autonomic neuropathy can occur, it is less common and less severe than that found with vATTR or AL disease.[17,18]

The median age of diagnosis is 74 years. Rarely, disease can be diagnosed as early as age 40.[18] While >90% of cases are found in Caucasian men, some series of hospitalized HFpEF have found equal male and female predominance of ATTR

BUY NOW

Because learning changes everything.®

mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.

Mc Graw Hill

FUSTER & HURST'S THE HEART 15TH EDITION



amyloidosis.[19] Hence, it is feasible referral bias leads to the impression of it being primarily a disease of older men.

## VARIANT TRANSTHYRETIN AMYLOIDOSIS

Over 130 point mutations in the TTR gene have been reported.[20] TTR mutations are inherited as autosomal-dominant mutations with a variable penetrance; although, in the majority of mutations, the penetrance is considered to be high. The point mutations result in kinetic instability of the transthyretin tetramer, resulting in dissociation into monomers and begin the misfolding process into the amyloid fibrils often earlier in life than wtATTR disease. It is paramount that any patient deemed to have ATTR versus AL disease undergo genetic testing. In addition to Val122Ile, common mutations in the United States include Thr60Ala (p.T80A), and Val30Met (p.V50M).[21] Val122Ile occurs in 3.4% of Black American population and is also found in people of African Caribbean and West African descent and leads to predominantly cardiac involvement with discovery often in a patient's sixties. History of carpal tunnel disease is common and peripheral length dependent sensorimotor neuropathy is rare. The presence of neuropathy however is important because it affects available therapeutic options. Within the Black American population, while the Val122Ile mutation is common, nearly 25% of call cases of ATTR cardiomyopathy will in fact be due to wtATTR disease. Thr60Ala is found in Irish Americans (originating in Donegal) and presents with a mixed cardiac and neuropathy phenotype and also often has antecedent carpal tunnel syndrome. Neuropathy symptoms often appear before HFpEF symptoms. Val30Met is actually the most common mutation worldwide and is endemic in Portugal, Japan, and Sweden leading to vATTR neuropathy. In nonendemic regions of the world, including the United States, Val30Met has a later-onset with a mixed but predominantly cardiac and neuropathic phenotype. Less common but important mutations include Ile68Leu (p.I88L) and Phe64Leu (p.F84L) from Italy, the latter of which has specific considerations during diagnostic workup.

## CLINICAL CHARACTERISTICS OF AMYLOID CARDIOMYOPATHIES

AL amyloidosis occurs in approximately 10 patients per million per year with no increase over time (based on reports from the US, Europe, and United Kingdom). Seventy percent of patients have cardiac involvement. The prevalence of variant ATTR cardiac amyloidosis is not known, but there is an estimated worldwide prevalence of 50,000 persons—20% with predominant polyneuropathy and 80% with predominant cardiomyopathy with mixed phenotypes of both in 60% to 70% of patients (Fig. 43–3)—and is likely to be underdiagnosed because the presentation is nonspecific. In AL amyloidosis, extracardiac involvement is very common, with 60% of patients having renal amyloid, 15% having autonomic or peripheral neuropathy, and 15% having hepatomegaly. Dental indentations in the tongue are only seen in AL amyloidosis and are present in approximately 15% of patients.

Sperry et al. found that among 98 patients with carpal tunnel syndrome undergoing tenosynovectomy, 10.2% stained positive for amyloid and can predate a diagnosed of cardiac amyloidosis by 5 to 10 years.[22] While most had wtATTR disease, two patients had vATTR and two patients had AL disease. Amyloid deposition in the ligamentum flavum can lead to spinal stenosis with worsening symptoms with age.[23]

Advances in noninvasive cardiac imaging and emergence of effective therapeutics have sparked interest in cardiac amyloidosis research in recent years. Several studies have demonstrated that cardiac amyloidosis is not a rare disease, as it was once thought, but rather a relatively common entity in certain well-defined patient groups. As previously mentioned, in a study of 108 patients with established HFpEF who underwent endomyocardial biopsy at Johns Hopkins, 15 (14%) patients were diagnosed with cardiac amyloidosis (7 with wtATTR, 4 with vATTR, 3 with AL, and 1 with AA).[11] In another study, of 120 consecutive patients (≥60 years) with hospitalized HFpEF undergoing 99mTc-DPD scintigraphy, 13% had radionuclide evidence of ATTR cardiac amyloidosis (all wild type).[19] Beyond HFpEF, older patients with aortic stenosis may be at high risk for comorbid wtATTR cardiomyopathy. Among 151 patients undergoing transcatheter aortic valve replacement, 24 patients (16%) were positive for TTR cardiac amyloidosis using 99mTc pyrophosphate scintigraphy. Most of these patients had a low-flow, low-gradient aortic stenosis due to decreased cardiac output and restrictive physiology.[24] In another study of 200 aortic stenosis patients aged ≥75 years referred for transcatheter intervention, 26 (13%) were found to have cardiac amyloidosis on a nuclear scan.[25] These studies strongly suggest that cardiac amyloidosis is an underdiagnosed entity, and a strong clinical suspicion is needed in specific patient groups, such as elderly patients with HFpEF and patients with aortic stenosis.

Because of the nonspecific symptomatology associated with cardiac amyloid, there is frequently a delay in diagnosis. Common cardiac misdiagnoses before consideration of ATTR cardiomyopathy include hypertrophic cardiomyopathy, hypertensive heart disease, or changes to the myocardium in patients with advanced/end-stage renal disease based on echo images. The median time from onset of symptoms is 6 to 12 months, but 10% of patients report a >3-year interval between symptoms and diagnosis and, in another 10%, 2 to 3 years between symptoms and diagnosis. Although 70% of patients with amyloidosis have cardiac involvement, only 19% of the diagnosing physicians are cardiologists.[26]

Cardiac amyloidosis should be suspected in a patient with left ventricular hypertrophy and reduced tolerance of antihypertensive medications over time. This reflects an inability to tolerate β-blockers and nondihydropyridine calcium channel blockers due to blunting of cardiac output with lowering of heart rate in patients with restrictive myopathies and a fixed stroke volume. Furthermore, vATTR cardiomyopathy patients often exhibit symptomatic orthostatic hypotension and syncope after taking angiotensin converting enzyme inhibitors or angiotensin receptor blockers due to neurohormonal insufficiency in the presence of autonomic dysfunction. Arrhythmias and conduction disturbances are frequent. Atrial fibrillation

BUY NOW

Because learning changes everything.®

mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.

Mc Graw Hill

FUSTER & HURST'S THE HEART 15TH EDITION



is common in AL and ATTR cardiomyopathy with the prevalence of comorbid disease often increasing with advancing age, which can exacerbate heart failure symptoms but may not impact survival.[27,28] In AL amyloidosis, sudden cardiac death represents electrical mechanical dissociation rather than ventricular tachycardia.[29]

## DIAGNOSTIC EVALUATION

A schematic on a way to approach patients that carry a suspicion of a diagnosis of cardiac amyloidosis is given in **Fig. 43–4**. An appropriate level of suspicion is the key in timely diagnosis of cardiac amyloidosis. Although the presence of noncardiac manifestations may provide the clue to diagnosis, many patients have symptoms and signs only attributed to cardiac involvement. Classical teaching dictates that patients with cardiac amyloidosis have low-voltage electrocardiograms (ECGs); however, less than 40% of patients have this finding and therefore this is not sensitive in ruling out disease.[30] A discrepancy between left ventricular wall thickening and voltage on ECGs as well as a pseudo-infarct pattern are more reliable ECG findings. Similarly, echocardiographic and magnetic resonance imaging (MRI) features suggestive of amyloid cardiomyopathy should be carefully evaluated.[31] Any patient with suspicion of cardiac amyloidosis should have serum-free light-chain assay and serum and urine immunofixation studies performed to assess for the presence of monoclonal process. Any lab abnormality should trigger referral to hematology/oncology for evaluation for AL disease. Biopsies to detect amyloid deposits in fat, bone marrow, or lip with Congo red staining and subsequent tissue typing by mass spectroscopy or immunohistochemistry would obviate the need for endomyocardial biopsy in most cases. Regarding AL cardiomyopathy specifically, a bone marrow biopsy is necessary to exclude multiple myeloma and will exhibit positive staining for AL disease in 50% cases. When combined with a subcutaneous fat aspirate, histologic diagnosis of AL disease can be confirmed in 85% of cases after mass spectroscopy or immunofluorescence subtyping. Of note, unfortunately, immunohistochemistry is limited by the size of the antibody panel, and the fact that amyloid proteins are frequently fragmented, having had the epitopes required for antibody recognition deleted.[32] Moreover, the protein misfolding that is characteristic of amyloid will often bury epitopes so that they are not visible to commercially provided antibodies and, as a consequence, immunohistochemistry or immuno-electron gold will be equivocal. Although not widely available and expensive, mass spectroscopic identification of the protein subunit remains the gold standard. In very large

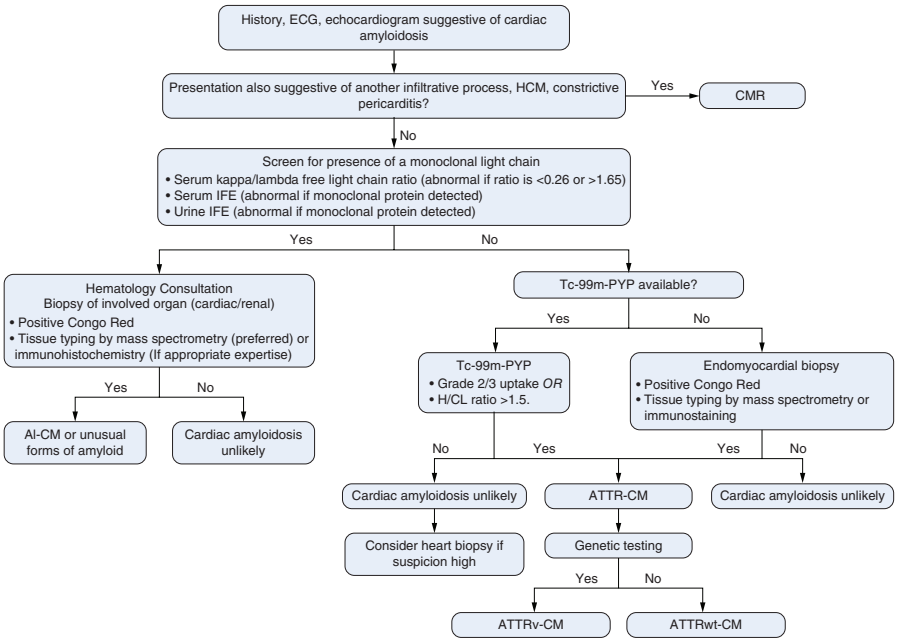



**Figure 43–4.** Schematic showing a diagnostic workup for cardiac amyloidosis. Reproduced with permission from Kittleson MM, Maurer MS, Ambardekar AV, et al: Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement From the American Heart Association, *Circulation*. 2020 Jul 7;142(1):e7-e22.

BUY NOW

Because learning changes everything.®

mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.

Mc Graw Hill

FUSTER & HURST'S THE HEART 15TH EDITION



studies, the technique is capable of identifying the protein subunit in 90% of patients and is quite specific.[33]

Endomyocardial biopsy would only be needed if such studies did not exhibit amyloid deposition to confirm AL cardiomyopathy or if despite recognition of a monoclonal process in extracardiac tissue, sufficient suspicion remains for the rare possibility of simultaneous of ATTR cardiomyopathy.[34]

In the absence of a monoclonal protein, nuclear scintigraphy with bone-avid tracers including Technetium-99m (Tc-99m)-pyrophosphate (PYP) in the United States and Tc-99m-3,3-disphosphono-1,2-propandicarboxylic acid (DPD) or Tc-99m-hydroxymethylene diphosphonate (HMDP) in Europe can be obtained to assess for ATTR cardiomyopathy. Should a scan exhibit uptake of the tracer, a diagnosis of ATTR cardiomyopathy can be made, at which point genetic screening should be performed because it has implications for available therapy and familial screening/early detection, regardless of the age of the patient. While fat pad biopsies are commonly performed to assess for systemic amyloidosis, in fact, they offer poor sensitivity to rule out vATTR and wtATTR disease with rates of 45% and 15%, respectively.[35] Nonetheless, gold standard diagnosis of cardiac amyloidosis requires a positive endomyocardial biopsy demonstrating Congo red birefringent deposits (Fig. 43–2) or sodium sulphate-Alcian Blue cardiac staining, with subsequent mass spectroscopic protein subunit typing to discriminate whether AL, wtATTR, vATTR, or other rare forms of amyloidosis are present.

## IMAGING

### Echocardiography

The standard diagnostic imaging for cardiac amyloidosis includes echocardiography as the first-line test. Most commonly, two-dimensional echocardiography reveals concentric thickening of the left ventricle (1.2 cm or greater) (**Fig. 43–5**). Occasionally, asymmetric thickening of the septum can be seen, which can phenotypically mimic hypertrophic cardiomyopathy. Abnormal "scintillating" bright echotexture of the left ventricular wall has been described but it is rarely clinically useful in the age of harmonic imaging causing the myocardium can be bright in a number of diagnoses that lead to left ventricular wall thickening including hypertensive heart

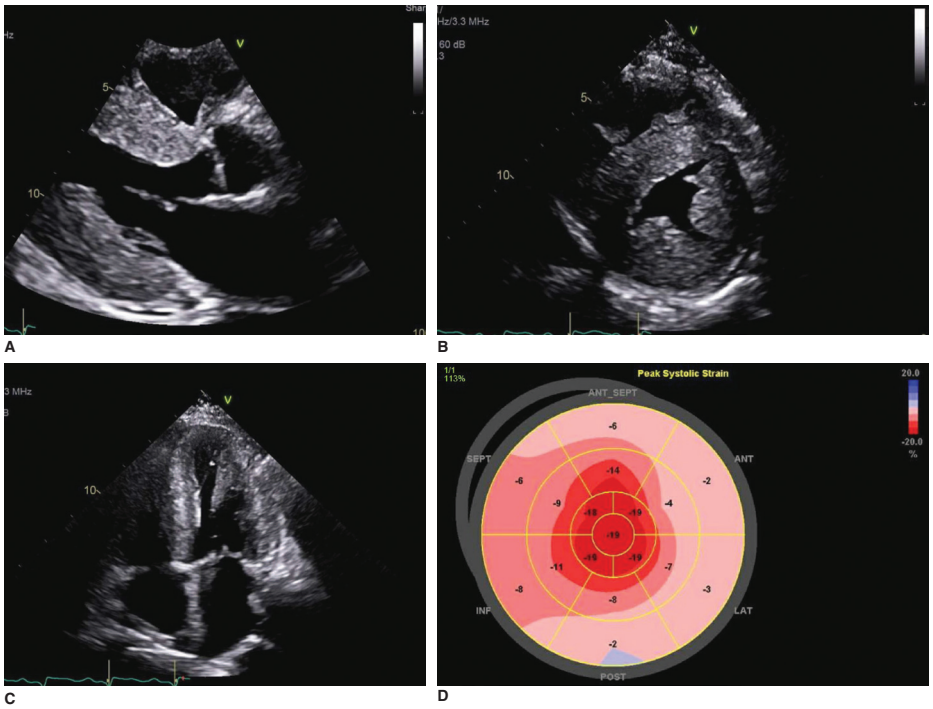



**Figure 43–5.** Characteristic two-dimensional echocardiographic images of cardiac amyloidosis in **(A)** parasternal long axis, **(B)** parasternal short axis, and **(C)** apical four chamber views notable for concentric left ventricular wall thickening and a "scintillating" myocardium. **(D)** Characteristic strain bull's eye plot showing a relative apical sparing pattern.

BUY NOW

Because learning changes everything.®

mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.

Mc Graw Hill

FUSTER & HURST'S THE HEART 15TH EDITION



disease, advanced/end-stage renal impairment, and lysosomal storage disease. Other echocardiographic findings include valvular thickening, right ventricular hypertrophy, and a small pericardial effusion. Aortic stenosis, specifically low-gradient, has been associated with TTR cardiac amyloidosis, and should raise clinical suspicion especially if the left ventricular cavity appears small. Left ventricular ejection fraction is typically preserved or mildly decreased but stroke volume index is commonly reduced due to concentric remodeling/hypertrophy. In one study, wall thickening and diastolic abnormalities were associated with a low amyloid burden, while left and right ventricular dysfunction as measured by left ventricular ejection fraction and tricuspid annular plane excursion, respectively, with advanced disease.[36]

Diastolic dysfunction is typical for patients with cardiac amyloidosis. Progressive biatrial enlargement is commonly seen. Mitral inflow with impaired relaxation pattern is seen at early stages; however, a restrictive pattern showing grade III diastolic dysfunction is often found at the time of diagnosis with blunted mitral annular tissue Doppler e' velocity resulting in very elevated E/e' values, signifying elevation in left ventricular filling pressures.[37] Pulmonary pressures may be elevated and can be estimated from TR velocities.

Myocardial deformation imaging and evaluation of diastolic function are important echocardiographic measures in these patients. Speckle tracking echocardiography allows reliable evaluation of myocardial function over the cardiac cycle by assessment of global longitudinal strain. Characteristically, patients with cardiac amyloidosis have significantly decreased global longitudinal strain despite preserved left ventricular ejection fraction. Regional deformation heterogeneity with reduction in strain in the base- and mid-myocardial segments and relative preservation of apical longitudinal strain can be seen resulting in relative apical-sparing or "cherry-on-top" pattern on a longitudinal strain bull's eye display[38] (Fig. 43–5). Such a deformation pattern can help differentiate cardiac amyloidosis from hypertrophic cardiomyopathy wherein the latter would show a decrement in strain only in the septum or areas with myocardial fiber disarray.[38] Although this regional deformation pattern has been promoted as characteristic, it may not be sensitive to rule out disease. In one study of patients with aortic stenosis and concomitant cardiac amyloidosis, this pattern was not universally predictive of cardiac amyloidosis.[24] Of note, while echocardiography can raise the index of suspicion for cardiac amyloidosis, it is not a clinically validated tool for diagnosis that can warrant treatment initiation or at this time differentiate between AL and ATTR disease.

## Cardiac Magnetic Resonance Imaging

MRI is an important imaging tool in assessing patients with suspected infiltrative cardiomyopathies including sarcoidosis, hemochromatosis, and Fabry's disease in addition to amyloidosis, since it provides structural, physiologic (volumes and flows), and tissue characterization data. MRI-derived chamber volumes and left ventricular mass show a high degree of reproducibility. Gadolinium-based contrast imaging allows detection of abnormal patterns that can be highly suggestive of cardiac amyloidosis, although they again do not discriminate between AL and ATTR disease and cannot at this time be used as a diagnostic tool to warrant treatment initiation by itself. Traditionally, inability to "null" the myocardium (to make it black by the operator) has been described as highly suggestive of cardiac amyloidosis. With phase-sensitive inversion recovery sequence, left ventricular late gadolinium enhancement is very common in these patients, and starts as diffuse subendocardial delayed enhancement but can produce to full thickness delayed enhancement in advanced disease (**Fig. 43–6**). Occasionally, patchy myocardial scar can be seen that is often attributed to cardiac sarcoidosis. Clues to amyloidosis include concomitant right ventricular thickening and delayed enhancement and biatrial enlargement and delayed enhancement. Late gadolinium enhancement has been shown to be a strong predictor of mortality with all typical subtypes of cardiac amyloidosis, especially with transmural enhancement.[39]

Parametric mapping provides unique insights into the disease process in patients with cardiac amyloidosis. Native T1 mapping does not require gadolinium-based contrast. T1 signal is significantly increased with amyloid deposition, which has been demonstrated both in patients with established amyloidosis and vATTR carriers. Postcontrast administration, T1 mapping, and extracellular volume estimation can be performed. Extracellular volume is markedly elevated in cardiac amyloidosis patients (often above 0.5), and it is considered the most reproducible MRI measure of amyloid burden.[40] Similarly, it has stronger prognostic and diagnostic values when compared to native and postcontrast T1 mapping and late gadolinium enhancement.[40,41] Extracellular volume can potentially identify early disease, risk stratify patients, and assess response to therapy in both AL and vATTR disease.[42,43] More studies are needed to define its role in routine patient management.

Obvious limitations of MRI imaging include presence of noncompatible metallic devices, significant renal dysfunction (for contrast administration), poor patient cooperation, and claustrophobia.

## Nuclear Imaging

Nuclear medicine techniques have revolutionized the way that patients with ATTR cardiomyopathy are diagnosed in daily practice; obviating the need for biopsy in many patients. Tc-99m PYP is commonly utilized in the United States while Tc-99m DPD and Tc-99m HMDP is used in Europe. On planar imaging, bone tracer uptake is commonly graded qualitatively with visual scores ranging from 0 to 3, where 0 indicates no cardiac uptake, 1 indicates cardiac uptake is less than rib uptake, 2 indicates cardiac uptake is equal to rib uptake, while 3 indicates strong cardiac uptake exceeding rib uptake by intensity (**Fig. 43–7**). A semiquantitative heart to contralateral lung uptake ratio can also be used (>1.5 at 1 hour is diagnostic). Planar imaging must be confirmed by single-photon emission computed tomography (SPECT) in all positive scans to confirm myocardial retention of the tracer as opposed to blood pool signal[44] (Fig. 43–7). There is a >99% sensitivity in cardiac

BUY NOW

Because learning changes everything.®

mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.

Mc Graw Hill

FUSTER & HURST'S THE HEART 15TH EDITION



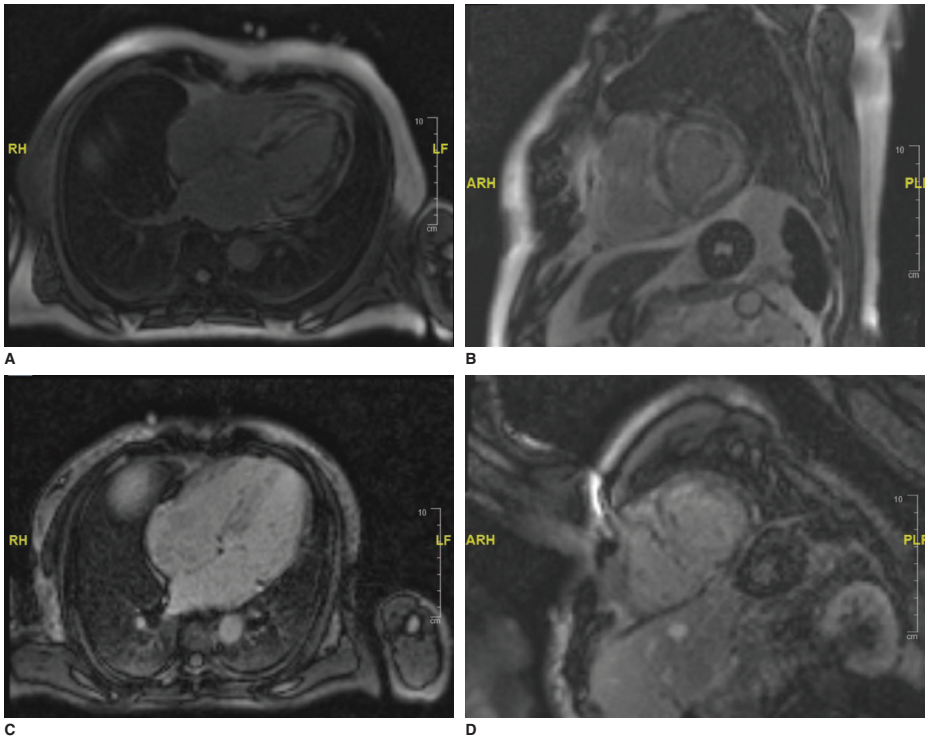



**Figure 43–6.** Two examples on cardiac MRI of early cardiac amyloidosis with subendocardial delayed enhancement (**A** and **B**) and late-stage disease showing full thickness delayed enhancement (**C** and **D**).

involvement detection in patients with ATTR amyloid, with a specificity of 86%.[45] Ninety-four percent of biopsy-proven cardiac ATTR had moderate-to-high uptake, where only 21% of patients with cardiac AL have this level of uptake, which can lead to false-positive scans. Thus, in the absence of a detectable monoclonal protein, a visual score of 2 or 3 or a heart to contralateral ratio >1.5 confirmed with SPECT is highly predictive of ATTR cardiomyopathy with specificity approaching 100%.[46] After diagnosis by nuclear scintigraphy, genetic testing can discriminate wtATTR versus vATTR cardiomyopathy.

False positives can still occur, however, in the presence of severe renal disease, significant coronary artery disease leading to focal uptake, hydroxychloroquine use in rheumatologic disorders, and ApoA4 cardiomyopathy. Of note, false negatives can occur with the Phe64Leu pathogenic variant for vATTR cardiomyopathy.[47] Thus, if the index of suspicion for cardiac amyloidosis is still high despite negative or equivocal results on nuclear scintigraphy or one is concerned about a false-positive scan, endomyocardial biopsy is needed to confirm a diagnosis.[44]

Investigational areas of nuclear imaging look to quantitate amyloid burden. Early data suggests that quantitative SPECT/CT imaging correlates well with planar bone avid imaging and may play a future role in assessing disease progression or response to therapy.[48] Amyloid-specific PET tracers (C-11 Pittsburgh-B compound, F-18-florbetapir) allow cardiac and whole-body direct visualization and potential quantification of amyloid fibril deposition.[49,50] While, these compounds are considered investigative and at this time cannot discriminate between amyloid subtypes, some potential PET tracers such as 18F-sodium fluoride may offer the ability to discriminate AL and ATTR amyloidosis when combined with cardiac MRI.[51]

## Cardiac CT imaging

Cardiac amyloidosis, specifically TTR subtype, appears to be prevalent in patients with aortic stenosis undergoing transcatheter valve replacement.[24] CT imaging is routinely obtained in patients referred for transcatheter intervention. Studies have shown that CT imaging allows extracellular volume quantification in these patients with minimal increase in acquisition time and radiation dose.[52] Expansion of extracellular volume as seen on CT imaging may allow efficient screening for comorbid cardiac amyloidosis among aortic stenosis patients considered

BUY NOW

Because learning changes everything.®

mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.

Mc Graw Hill



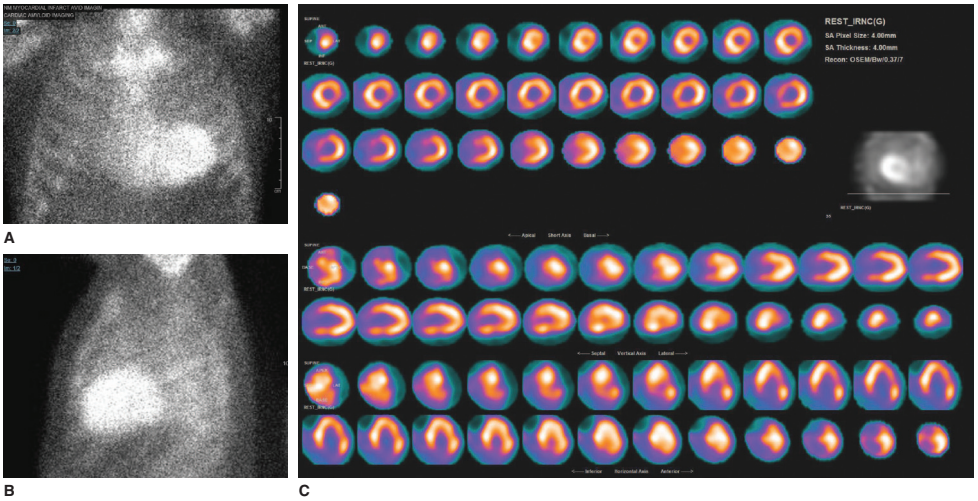



**Figure 43–7.** Tc-99m PYP scan showing qualitative Grade III uptake on planar images (**A** and **B**) with confirmation of myocardial tracer retention on (**C**) SPECT imaging consistent with a diagnosis of ATTR cardiomyopathy.

for transcatheter intervention. Nonetheless, validation of ATTR cardiomyopathy would still entail either endomyocardial biopsy or positive bone avid Tc-99m scintigraphy in the absence of a monoclonal protein.

## CARDIAC BIOMARKERS AND STAGING CARDIAC AMYLOIDOSIS

Once diagnosed, staging helps prognosticate disease. Two scoring systems help prognosticate wtATTR cardiomyopathy: the Mayo wtATTR staging system and the United Kingdom National Amyloidosis Centre staging system (**Table 43–2**). In the Mayo scoring system, one point is assigned for an NT-proBNP >3000 pg/mL and one point is assigned for a troponin T of >0.05 ng/mL (or high-sensitivity cardiac Troponin T >65 ng/L). Stage 1 disease reflects 0 points, Stage 2 reflects 1 point, and Stage 3 reflects 2 points. The median survival of patients with Stage 1, 2, and 3 disease, respectively, is 66, 42, and 20 months.[53] Alternatively, the National Amyloidosis Centre scoring system utilizes eGFR <45 mL/min/1.73 $m^2$ in lieu of Troponin T measurements and applies to both wtATTR and vATTR cardiomyopathy and has similar median survivals for Stage 1, 2, and 3 disease at 69.2, 46.7, and 24.1 months, respectively.[54]

In AL amyloidosis, the staging system utilizes 3 classes of biomarkers including NT-proBNP ≥1800 pg/mL (or BNP ≥400 ng/L), cardiac troponin T >0.025 ng/mL (or high-sensitivity cardiac troponin T ≥40 ng/L), and the serum-free light-chain difference between involved and uninvolved light chains of >180 mg/L (Table 43–2). A point is assigned for each factor above the thresholds, resulting in four stages, with median survivals of 73, 35, 15, and 5 months, respectively, which is

**TABLE 43–2. Staging of Cardiac Amyloidosis**

| | Mayo Staging | Mayo Staging | UK National Amyloidosis Centre |
|---|---|---|---|
| Population | Light Chain | Wildtype Transthyretin | Wild-Type and Variant Transthyretin |
| Parameters | NT-proBNP <1800 pg/mL<br>Troponin T ≤0.025 ng/mL<br>Serum Light Chain Difference <180 mg/L | NT-proBNP <3000 pg/mL<br>Troponin T ≤0.05 ng/mL | NT-proBNP <3000 pg/mL<br>eGFR ≥45 mL/min |
| Median Survival | | | |
| Stage 1: all parameters normal | 73 months | 66 months | 69.2 months |
| Stage 2: 1 parameter abnormal | 35 months | 40 months | 46.7 months |
| Stage 3: 2 parameters abnormal | 15 months | 20 months | 24.1 months |
| Stage 4: 3 parameters abnormal | 5 months | N/A | N/A |

BUY NOW

Because learning changes everything.®

mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.

Mc Graw Hill

FUSTER & HURST'S THE HEART 15TH EDITION



far shorter than TTR amyloidosis.[55] In AL amyloidosis, multiple organ involvement carries an inferior prognosis. Genetic abnormalities in the plasma cells, such as t(11;14), may predict resistance to bortezomib chemotherapy and inferior prognosis, and deletion of 17p, which suggests that chemotherapy drug resistance or short response to chemotherapy are important tests performed on a patient's bone marrow in AL amyloidosis.[56,57]

## THERAPY

### Heart Failure

Maintaining euvolemia via diet control and loop diuretics remains the cornerstone of congestive symptoms for cardiac amyloidosis. Higher bioavailability of torsemide and bumetanide make them preferable over furosemide and can be used in conjunction with high dose aldosterone antagonists for volume management. There is no current recommended goal-directed medical therapy for cardiac amyloidosis. Common agents used for HFrEF or diagnoses that are often confused with cardiac amyloidosis such as hypertensive heart disease and hypertrophic cardiomyopathy can be deleterious. In the setting of a fixed stroke volume, patients with advanced cardiac amyloidosis often have lower blood pressures from reduce ventricular capacitance and ventricular vascular coupling.[58] Higher heart rates maintain cardiac output and hence patients with cardiac amyloidosis do not feel well when β-blockers are used to excessively blunt heart rate. Relative neurohormonal insufficiency and autonomic dysfunction, especially in AL and vATTR systemic amyloidosis, can lead to symptomatic orthostatic hypotension with the use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Furthermore, nondihydropyridine calcium channel blockers are avoided due to older case reports of shock in patients with systemic AL disease.[59] To maintain adequate blood pressure and preload in the setting of advanced disease, compression stockings and midodrine can be helpful. In the subset of patients with comorbid aortic stenosis and ATTR cardiomyopathy that could be exacerbating heart failure, early data shows that transcatheter valve replacement significantly improves one to two year outcomes.[25]

### Arrhythmia and Device Therapy

Patients with cardiac amyloidosis often have comorbid and symptomatic atrial fibrillation. Balancing heart rate to control atrial fibrillation without blunting cardiac output can pose challenges. As aforementioned, lowering β-blockers to the lowest acceptable dose to avoid excessive heart rate control is preferable.

Despite literature to the contrary, the use of digoxin, in an effort to control atrial fibrillation rate in carefully selected patients, can be very effective and does not produce excessive toxicity in cardiac amyloidosis.[60] Amiodarone can be used in the treatment of supraventricular arrhythmias in amyloidosis patients.[28,61] Along with cardioversion and ablative therapy, this is more effective earlier in the disease course when trying to restore sinus rhythm.[28] Given propensity to form intracardiac thrombi, even in sinus rhythm, anticoagulation is preferred, either with coumadin or direct oral anticoagulants, at any CHADs-VASc score to attenuate stroke risk.[62]

Heart block due to conduction system should be suspected and investigated with Holter and event monitoring if patients present with syncope. Pacemaker implantation should follow the recommendations of the American College of Cardiology/American Heart Association/Heart Rhythm Society.[53] In a retrospective observational study of 78 patients with ATTR cardiac amyloidosis, with an implantable device, worsening mitral regurgitation was seen in 11% of patients with right ventricular pacing <40%. Furthermore worsening left ventricular ejection fraction and New York Heart Association functional class occurred in 26% and 22% of patients who were right ventricular paced <40% of the time and increased to 89% for both when right ventricular paced >40% of the time.[63] Should patients meet an indication, biventricular pacing can be considered in patients with ATTR cardiac amyloidosis to achieve higher heart rates and theoretically higher cardiac output. Further study is needed to determine if such interventions lead to overall improvement symptoms and mortality in patients with chronotropic incompetence or heart block and cardiac amyloidosis.

At this time, data on the use of primary prevention implantable cardiac defibrillators (ICD) is controversial given lack of survival benefit. Literature, however, may be biased based on prior limited survival without effective therapies or late stage diagnoses of both AL and ATTR cardiomyopathy. Death in patients with AL disease may in fact be due to electromechanical dissociation as well as to a primary arrhythmic etiology.[64] In carefully selected patients with estimated survival >1 year or those who may be awaiting organ transplantation, ICDs can be placed for secondary prevention of sudden cardiac death due to ventricular arrhythmias.[65]

### Anti-Amyloid Therapy for AL

Chemotherapy is the mainstay of treatment for AL amyloidosis. The source of the amyloid deposits are clonal plasma cells in the bone marrow, and elimination of these plasma cells using anti-plasma cell chemotherapy has been the standard of care for 50 years. Initially, melphalan and prednisone was used but produced only occasional responses, and the responses were not prolonged. In 1985, myeloablative chemotherapy with autologous stem cell transplantation was introduced for the treatment of amyloidosis and has shown to be an effective technique, capable of very profound responses that were durable, with 15-year survivors being reported. Stem cell transplantation in patients with cardiac amyloidosis, however, carries mortality rates that are reported as high as 10%, which would be unacceptable in the modern era now that there are alternative drugs available.[66] Selection of patients with cardiac amyloidosis for stem cell transplantation is best done at a large center, but typical inclusion criteria include a patient that is ambulatory more than 50% of the day, a systolic blood pressure of >90 mm Hg and serum creatinine <2 mg/dL, and high-sensitivity troponin T <75 ng. With these criteria, transplant-related mortality is approximately 2.5%, with hematologic response rates of 66% and cardiac response rates (30% reduction of NT-proBNP) of

BUY NOW

Because learning changes everything.®

mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.

Mc Graw Hill

FUSTER & HURST'S THE HEART 15TH EDITION



41%. Ten-year survival after stem cell transplant is 25% but is 53% in patients that achieve a complete response.[67]

For nontransplant-eligible patients, the standard of care is bortezomib-based chemotherapy leading to hematologic response in 77% of cases and complete response in 16% of cases. Bortezomib is administered once a week subcutaneously. In a study of 230 AL patients treated with cyclophosphamide, bortezomib, and dexamethasone (CyBorD), the hematologic response rate was 60%, with a cardiac response in 17% of patients, and a renal response in 25% of patients.[68]

The anti CD-38 monoclonal antibody, daratumumab, is highly effective in the treatment of AL amyloidosis. Single center data from the Mayo Clinic using daratumumab-based therapy in 41 patients with relapsed or refractory AL amyloidosis yielded hematologic response in 80% of patients and cardiac response in 33% of patients after a median follow-up of 7.5 months.[69] The ANDROMEDA study showed the completed response rate to be 53.3 vs 18.1% favoring daratumumab. The cardiac response rate in the groups was 41.5 vs 22.2% favoring daratumumab.[70]

### Treatment of ATTR

Clinical and investigational therapies for TTR amyloidosis is based on either (1) silencing production of the TTR protein, (2) stabilization of the TTR tetramer, or (3) disruption or extraction of the TTR amyloid fibrils.

The only current approved for therapy ATTR cardiomyopathy in the United States is the TTR tetramer stabilizing compound tafamidis that binds with high affinity to the thyroxine binding site on TTR, largely preventing kinetic destabilization and rearrangement into amyloid fibrils and has virtually no side effect profile. Tafamidis meglumine (20 mg or 80 mg) was tested against placebo in the 2018 randomized controlled ATTR-ACT trial in patients with wtATTR and vATTR cardiomyopathy.[71] The primary hierarchal endpoint of first, all-cause mortality and secondly, rates of cardiovascular hospitalizations using the Finkelstein–Schoenfeld method yielded a "win ratio" of tafamidis over placebo of 1.70 ($P = 0.0006$) for reducing such events.[72] Secondary endpoints of the primary outcomes using Kaplan–Meier time-to-event analysis yielded a 30% reduction in the hazard for all-cause mortality and 32% reduction hazard for cardiovascular hospitalization in patients randomized to tafamidis (pooled 20 mg and 80 mg doses) to placebo. Furthermore, tafamidis resulted in much slower decline in 6-minute walk test distances and Kansas City Cardiomyopathy Questionnaire Scores compared to placebo. While data exists showing that tafamidis can slow the progression of vATTR polyneuropathy,[73] at this time tafamidis only carries an indication for vATTR polyneuropathy outside of the Unites States in Europe and Japan.

AG10 (acoramidis) is a TTR stabilization based on coinheritance of the Thr119Met mutation leading to natural stabilization of the TTR tetramer and is in phase-3 clinical trial testing for wtATTR and vATTR cardiomyopathy (ATTRIBUTE-CM [Efficacy and Safety of AG10 in Subjects with Transthyretin Amyloid Cardiomyopathy]; ClinicalTrials.gov. NCT03860935). It showed a favorable safety profile in Phase 2 testing with near complete TTR stabilization and open label extension data showed that this led to lower mortality and cardiovascular hospitalizations over 15 months.[74]

TTR stabilization can also be achieved with off-label use of the nonsteroidal anti-inflammatory drug diflunisal 250 mg twice a day with only single-center studies showing effectiveness for wtATTR and vATTR cardiomyopathy at this time.[75-77] While rare, diflunisal can result in a small reduction in estimated glomerular filtration rate and slightly increased rates of gastrointestinal complaints, but can be a much more affordable alternative to tafamidis. Notably, response to TTR stabilizers including tafamidis, off-label diflunisal, and under investigation AG10 can be assessed by measurement of serum prealbumin (transthyretin levels), which measures stable transthyretin tetramer conformations as opposed to unstable-dissociated transthyretin monomer subunits.[74]

TTR silencers target hepatic synthesis of the TTR protein. Two currently available silencers are patisiran, an intravenously administered small interfering RNA that targets the TTR mRNA for degradation, and inotersen, a subcutaneously administered antisense oligonucleotide that binds TTR mRNA leading to its degradation. Patisiran and inotersen proved to be efficacious in the randomized APOLLO and NEURO-TTR studies, respectively, assessing for improvements in the Norfolk Quality of Life diabetic neuropathy and mNIS+7 neuropathy scores among patients with vATTR polyneuropathy.[78,79] Prespecificed cardiac substudies of patisiran from APOLLO noted that among individuals who had concomitant vATTR cardiomyopathy, treatment with patisiran led to less deterioration of global longitudinal strain, regression of LV wall thickening, and reduction in NT-proBNP.[80,81] Limited data also shows that inotersen may stabilize 6-minute walk test results, global longitudinal strain on echo, and lead to wall regression on cardiac MRI in patients with ATTR cardiomyopathy.[82,83] Of note, inotersen requires frequent monitoring of platelet count and serum creatinine due to rare side effects of fatal thrombocytopenia leading to intracranial hemorrhage and glomerulonephritis. Potential use of silencer therapy for ATTR cardiomyopathy at this time is limited to patients who otherwise have an indication for treatment for vATTR neuropathy. Ongoing clinical studies are assessing the utility of patisiran and inotersen for both wtATTR and vATTR cardiomyopathy and may give insight into the benefit of combination TTR silencer and TTR stabilizer therapy. These include APOLLO-B (A Study to Evaluate Patisiran in Participants with Transthyretin Amyloidosis with Cardiomyopathy; ClinicalTrials.gov. NCT03997383) and 24 Month Open Label Study of the Tolerability and Efficacy of Inotersen in TTR Amyloid Cardiomyopathy Patients (ClinicalTrials.gov. NCT03702829). Furthermore, next generation TTR silencer platforms for ATTR cardiomyopathy with easier administration and potentially less side effects are being tested in phase-3 trials, including HELIOS-B (A Study to Evaluate Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy; ClinicalTrials.gov. NCT04153149) and CARDIO-TTRansform (A Study to Evaluate the Efficacy and Safety of AKCEA-TTR-LRx in Participants with Transthyretin Mediated Amyloid Cardiomyopathy; ClinicalTrials.gov.

BUY NOW

Because learning changes everything.®

mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.

Mc Graw Hill

FUSTER & HURST'S THE HEART 15TH EDITION



NCT04136171). If in fact ATTR cardiomyopathy is seen as part of a spectrum of systemic TTR amyloidosis rather than as a distinct disease process by regulatory bodies, such therapies bear clinical weight for a spectrum of disease manifestations.

Lastly, TTR disruptive therapy aims to remove amyloid fibers from organ tissue after deposition. Conflicting evidence exists for the combination of doxycycline and tauroursodeoxycholic acid for TTR disruption.[84,85] The use of monoclonal antibodies targeting portions of deposited ATTR fibers is under investigation.[86]

### Advanced Heart Failure Therapies

ACC/AHA Stage D Heart Failure in patients with cardiac amyloidosis poses unique challenges when considering advanced therapies. Given the marked left ventricular hypertrophy, small left ventricular cavity size, and concomitant right ventricular dysfunction, limited data exists for the use of durable univentricular mechanical support with contemporary left ventricular assist devices.[87]

Heart transplantation for cardiac amyloidosis is possible for Stage D cardiac amyloidosis. The updated adult donor allocation system provides a status 4 designation to patients with cardiac amyloidosis given the lack of durable mechanical support options to reduce waiting times on the transplant list. In carefully selected patients, should mechanical support be needed as a bridge to cardiac transplantation, some data supports the use biventricular support either using biventricular extracorporeal devices or a total artificial heart.[88] Such patients would receive a status 2 designation on the transplant waiting list. Recent single-center studies show improving 1-year survival postcardiac transplantation of carefully selected candidates for both AL and ATTR cardiac amyloidosis, with and without biventricular mechanical support, and similar survival rates in patients transplanted for causes other than cardiac amyloidosis.[89,90] However, more data is needed across multiple institutions.

There are special considerations for transplant for both end-stage AL and ATTR cardiomyopathy. In the case of ATTR cardiomyopathy, age is often a limiting factor given the late development of advanced cardiomyopathy in individuals with Stage D heart failure. In the case of vATTR, concomitant neuropathy may affect posttransplant outcomes. Isolated liver transplantation to address vATTR cardiomyopathy and neuropathy, in order to diminish production of a kinetically unstable TTR protein, is not advisable given the possibility of progression of wtATTR deposition on prior sites of vATTR deposition and otherwise would be high risk in the setting of end-stage heart failure.[91,92] The need for combined heart–liver dual organ transplantation to remove mutant TTR from the blood and prevent progression of neuropathy post–heart transplantation has less scope in the new era of TTR silencer therapy, which may have an increasing role post–isolated heart transplantation.

Furthermore, in select patients with end-stage heart failure due to AL cardiomyopathy, cardiac transplantation can be considered if there is evidence of limited extracardiac organ involvement and patients show adequate nutritional status or lack of malabsorption. Standard chemotherapy regimens with proteosome inhibitor therapy and anti-CD-38 monoclonal antibody therapy with daratumumab should be given to target the clonal plasma cell. Once hematologic response is achieved post–heart transplant, there has been a shift in practice paradigms over the last 15 years in some centers in addressing recurrence of light-chain elevation. While some literature supports the use of stem cell transplantation as consolidative therapy when stable post–heart transplant (usually >6 months), use of proteosome inhibitor therapy and/or daratumumab can be achieved to attain hematologic response.[89]

## SUMMARY

There is a major educational gap in the diagnosis of cardiac amyloidosis with frequent confusion between amyloid infiltrative cardiomyopathy and hypertensive heart disease or other causes of HFpEF. Failure to incorporate immunoglobulin-free light-chain testing in the workflow of evaluation of patients with thickened heart walls runs the risk of missing the diagnosis of AL amyloidosis. In ATTR amyloidosis, incorporation of the nuclear scan with bone-avid tracers is vital in making a definitive diagnosis. Screening of the TTR gene for mutations helps distinguish wild-type from mutant TTR amyloidosis. Diagnosis is more important than ever since there are now a wide array of effective therapies for AL amyloidosis, two new therapies for the treatment of mutant ATTR amyloidosis, and oral therapy for wtATTR amyloidosis. Key summary differences in TTR

**TABLE 43-3. Key Differences in Disease Etiology, Diagnosis, and Management of Transthyretin Cardiac Amyloidosis Between the United States and Europe Based on the Transthyretin Amyloidosis Outcomes Survey and Expert Consensus Statements and Clinical Practice Updates From the American Heart Association and European Society of Cardiology**

| Parameter | United States | Europe |
|---|---|---|
| Percent wild-type | 48% | 25% |
| Notable pathogenic vATTR mutations | Val122Ile (p.V142I)<br>Thr60Ala (p.T80A)<br>Val30Met (p.V50M)-late onset | Leu111Met (p.L131M)<br>Ile68Leu (p.I88L)<br>Thr60Ala (p.T80A)<br>Val30Met (p.V50M)-early onset<br>Phe64Leu (p.F84L)<br>Ile107Val (p.I127V) |
| Tracers for nuclear scintigraphy and non-biopsy diagnosis | Pyrophosphate (PYP) | 3,3-disphospho-no-1,2-propandicarboxylic acid (DPD)<br>Hydroxymethylene diphosphonate (HMDP) |
| Recommended therapy | Tafamidis | Tafamidis |
| Alternative/adjunct therapies | Diflunisal (off-label)<br>Patisiran (if vATTR with neuropathy)<br>Inotersen (if vATTR with neuropathy) | Diflunisal (off-label) |

BUY NOW

Because learning changes everything.®

mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.

Mc Graw Hill

FUSTER & HURST'S THE HEART 15TH EDITION



cardiac amyloidosis disease etiology, diagnosis, and management based on the Transthyretin Amyloidosis Outcomes Survey and recent statements and practice updates from the American Heart Association/European Society of Cardiology are provided for reference in **Table 43–3.**[5,21,93,94]

- Cardiac amyloidosis is a leading cause of HFpEF. It may be confused with hypertrophic cardiomyopathy or hypertensive heart disease.
- Cardiac MRI and strain echocardiography may demonstrate findings that can lead to an early diagnosis.
- Abnormality in the immunoglobulin-free light-chain levels is an important clue to the presence of AL amyloidosis and should be checked in the workup of cardiac amyloidosis.
- Technetium pyrophosphate imaging is highly sensitive and specific in the diagnosis of TTR cardiac amyloidosis provided no monoclonal protein is detected.
- Systemic chemotherapy and stem cell transplantation directed at the plasma cell clone is effective therapy in cardiac AL amyloidosis.
- TTR silencers are currently approved only for vATTR polyneuropathy, with and without concomitant cardiomyopathy. Their use in cardiomyopathy is currently in Phase 3 testing.
- Tafamidis, a TTR stabilizer, improved survival in both wtATTR and vATTR cardiomyopathy and is the only approved therapy in the United States at this time for ATTR cardiomyopathy.

## REFERENCES


1. Aterman K. A historical note on the iodine-sulphuric acid reaction of amyloid. *Histochemistry* 1976;49:131-143.
2. Kyle RA. Amyloidosis: a convoluted story. *Br J Haematol*. 2001;114:529-538.
3. Muchtar E, Dispenzieri A, Magen H, et al. Systemic amyloidosis from A (AA) to T (ATTR): a review. *J Intern Med*. 2020;289(3):268-292.
4. Buxbaum JN, Ruberg FL. Transthyretin V122I (pV142I)* cardiac amyloidosis: an age-dependent autosomal dominant cardiomyopathy too common to be overlooked as a cause of significant heart disease in elderly African Americans. *Genet Med*. 2017;19:733-742.
5. Kittleson MM, Maurer MS, Ambardekar AV, et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. *Circulation* 2020;142:e7-e22.
6. Sukhacheva TV, Eremeeva MV, Ibragimova AG, Vaskovskii VA, Serov RA, Revishvili A. Isolated atrial amyloidosis in patients with various types of atrial fibrillation. *Bull Exp Biol Med*. 2016;160:844-849.
7. Gertz MA. Immunoglobulin light chain amyloidosis: 2018 Update on diagnosis, prognosis, and treatment. *Am J Hematol*. 2018;93:1169-1180.
8. Schmidt HH, Waddington-Cruz M, Botteman MF, et al. Estimating the global prevalence of transthyretin familial amyloid polyneuropathy. *Muscle Nerve* 2018;57:829-837.
9. Tanskanen M, Peuralinna T, Polvikoski T, et al. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. *Ann Med*. 2008;40:232-239.
10. Mitter SS, Pinney SP. Advances in the management of acute decompensated heart failure. *Med Clin North Am*. 2020;104:601-614.
11. Hahn VS, Yanek LR, Vaishnav J, et al. Endomyocardial biopsy characterization of heart failure with preserved ejection fraction and prevalence of cardiac amyloidosis. *JACC Heart Fail*. 2020;8:712-724.
12. Sidiqi MH, Aljama MA, Muchtar E, et al. Light chain type predicts organ involvement and survival in AL amyloidosis patients receiving stem cell transplantation. *Blood Adv*. 2018;2:769-776.
13. Keren DF, Schroeder L. Challenges of measuring monoclonal proteins in serum. *Clin Chem Lab Med*. 2016;54:947-961.
14. Basset M, Defrancesco I, Milani P, et al. Nonlymphoplasmacytic lymphomas associated with light-chain amyloidosis. *Blood* 2020;135:293-296.
15. Geller HI, Singh A, Alexander KM, Mirto TM, Falk RH. Association between ruptured distal biceps tendon and wild-type transthyretin cardiac amyloidosis. *JAMA* 2017;318:962-963.
16. Westermark P, Westermark GT, Suhr OB, Berg S. Transthyretin-derived amyloidosis: probably a common cause of lumbar spinal stenosis. *Ups J Med Sci*. 2014;119:223-228.
17. Connors LH, Sam F, Skinner M, et al. Heart failure resulting from age-related cardiac amyloid disease associated with wild-type transthyretin: a prospective, observational cohort study. *Circulation* 2016;133:282-290.
18. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2019;73:2872-2891.
19. Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J*. 2015;36:2585-2594.
20. Adams D, Koike H, Slama M, Coelho T. Hereditary transthyretin amyloidosis: a model of medical progress for a fatal disease. *Nat Rev Neurol*. 2019;15:387-404.
21. Maurer MS, Hanna M, Grogan M, et al. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol*. 2016;68:161-172.
22. Sperry BW, Reyes BA, Ikram A, et al. Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release. *J Am Coll Cardiol*. 2018;72:2040-2050.
23. Yanagisawa A, Ueda M, Sueyoshi T, et al. Amyloid deposits derived from transthyretin in the ligamentum flavum as related to lumbar spinal canal stenosis. *Mod Pathol*. 2015;28:201-207.
24. Castano A, Narotsky DL, Hamid N, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J*. 2017;38:2879-2887.
25. Scully PR, Patel KP, Treibel TA, et al. Prevalence and outcome of dual aortic stenosis and cardiac amyloid pathology in patients referred for transcatheter aortic valve implantation. *Eur Heart J*. 2020;41:2759-2767.
26. McCausland KL, White MK, Guthrie SD, et al. Light chain (AL) amyloidosis: the journey to diagnosis. *Patient* 2018;11:207-216.
27. Longhi S, Quarta CC, Milandri A, et al. Atrial fibrillation in amyloidotic cardiomyopathy: prevalence, incidence, risk factors and prognostic role. *Amyloid* 2015;22:147-155.
28. Donnellan E, Wazni OM, Hanna M, et al. Atrial fibrillation in transthyretin cardiac amyloidosis: predictors, prevalence, and efficacy of rhythm control strategies. *JACC Clin Electrophysiol*. 2020;6:1118-1127.
29. John RM. Arrhythmias in Cardiac Amyloidosis. *J Innov Card Rhythm Manag*. 2018;15;9(3):3051-3057.
30. Rapezzi C, Merlini G, Quarta CC, et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. *Circulation* 2009;120:1203-1212.
31. Witteles RM, Bokhari S, Damy T, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. *JACC Heart Fail*. 2019;7:709-716.
32. Winter M, Tholey A, Kristen A, Rocken C. MALDI mass spectrometry imaging: a novel tool for the identification and classification of amyloidosis. *Proteomics* 2017;17.


BUY NOW

Because learning changes everything.®

mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.

Mc Graw Hill

FUSTER & HURST'S THE HEART 15TH EDITION




33. Abildgaard N, Rojek AM, Moller HE, et al. Immunoelectron microscopy and mass spectrometry for classification of amyloid deposits. *Amyloid* 2020;27:59-66.
34. Fine NM. Challenges and strategies in the diagnosis of cardiac amyloidosis. *Can J Cardiol*. 2020;36:441-443.
35. Quarta CC, Gonzalez-Lopez E, Gilbertson JA, et al. Diagnostic sensitivity of abdominal fat aspiration in cardiac amyloidosis. *Eur Heart J*. 2017;38:1905-1908.
36. Boldrini M, Cappelli F, Chacko L, et al. Multiparametric echocardiography scores for the diagnosis of cardiac amyloidosis. *JACC Cardiovasc Imaging* 2020;13:909-920.
37. Mitter SS, Shah SJ, Thomas JD. A test in context: E/A and E/e' to assess diastolic dysfunction and LV filling pressure. *J Am Coll Cardiol*. 2017;69:1451-1464.
38. Phelan D, Collier P, Thavendiranathan P, et al. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. *Heart* 2012;98:1442-1448.
39. Fontana M, Pica S, Reant P, et al. Prognostic value of late gadolinium enhancement cardiovascular magnetic resonance in cardiac amyloidosis. *Circulation* 2015;132:1570-1579.
40. Martinez-Naharro A, Kotecha T, Norrington K, et al. Native T1 and extracellular volume in transthyretin amyloidosis. *JACC Cardiovasc Imaging* 2019;12:810-819.
41. Pan JA, Kerwin MJ, Salerno M. Native T1 mapping, extracellular volume mapping, and late gadolinium enhancement in cardiac amyloidosis: a meta-analysis. *JACC Cardiovasc Imaging* 2020;13:1299-1310.
42. Martinez-Naharro A, Abdel-Gadir A, Treibel TA, et al. CMR-verified regression of cardiac AL amyloid after chemotherapy. *JACC Cardiovasc Imaging* 2018;11:152-154.
43. Fontana M, Martinez-Naharro A, Chacko L, et al. Reduction in CMR derived extracellular volume with patisiran indicates cardiac amyloid regression. *JACC Cardiovasc Imaging* 2020.
44. Hanna M, Ruberg FL, Maurer MS, et al. Cardiac scintigraphy with technetium-99m-labeled bone-seeking tracers for suspected amyloidosis: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2020;75:2851-2862.
45. Castano A, Haq M, Narotsky DL, et al. Multicenter study of planar technetium 99m pyrophosphate cardiac imaging: predicting survival for patients with ATTR cardiac amyloidosis. *JAMA Cardiol*. 2016;1:880-889.
46. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation* 2016;133:2404-2412.
47. Musumeci MB, Cappelli F, Russo D, et al. Low sensitivity of bone scintigraphy in detecting Phe64Leu mutation-related transthyretin cardiac amyloidosis. *JACC Cardiovasc Imaging* 2020;13:1314-1321.
48. Scully PR, Morris E, Patel KP, et al. DPD quantification in cardiac amyloidosis: a novel imaging biomarker. *JACC Cardiovasc Imaging* 2020;13:1353-1363.
49. Gallegos C, Miller EJ. Advances in PET-based cardiac amyloid radiotracers. *Curr Cardiol Rep*. 2020;22:40.
50. Manwani R, Page J, Lane T, et al. A pilot study demonstrating cardiac uptake with 18F-florbetapir PET in AL amyloidosis patients with cardiac involvement. *Amyloid* 2018;25:247-252.
51. Trivieri MG, Dweck MR, Abgral R, et al. (18)F-sodium fluoride PET/MR for the assessment of cardiac amyloidosis. *J Am Coll Cardiol*. 2016;68:2712-2714.
52. Scully PR, Patel KP, Saberwal B, et al. Identifying cardiac amyloid in aortic stenosis: ECV quantification by CT in TAVR patients. *JACC Cardiovasc Imaging* 2020;13:2177-2189.
53. Grogan M, Scott CG, Kyle RA, et al. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. *J Am Coll Cardiol*. 2016;68:1014-1020.
54. Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J*. 2018;39:2799-2806.
55. Kumar SK, Gertz MA, Dispenzieri A. Validation of Mayo Clinic staging system for light chain amyloidosis with high-sensitivity troponin. *J Clin Oncol*. 2019;37:171-173.
56. Dumas B, Yameen H, Sarosiek S, Sloan JM, Sanchorawala V. Presence of t(11;14) in AL amyloidosis as a marker of response when treated with a bortezomib-based regimen. *Amyloid* 2020:1-6.
57. Wong SW, Hegenbart U, Palladini G, et al. Outcome of patients with newly diagnosed systemic light-chain amyloidosis associated with deletion of 17p. *Clin Lymphoma Myeloma Leuk*. 2018;18:e493-e499.
58. Bhuiyan T, Helmke S, Patel AR, et al. Pressure-volume relationships in patients with transthyretin (ATTR) cardiac amyloidosis secondary to V122I mutations and wild-type transthyretin: Transthyretin Cardiac Amyloid Study (TRACS). *Circ Heart Fail*. 2011;4:121-128.
59. Pollak A, Falk RH. Left ventricular systolic dysfunction precipitated by verapamil in cardiac amyloidosis. *Chest* 1993;104:618-620.
60. Donnelly JP, Sperry BW, Gabrovsek A, et al. Digoxin use in cardiac amyloidosis. *Am J Cardiol*. 2020;133:134-138.
61. Mints YY, Doros G, Berk JL, Connors LH, Ruberg FL. Features of atrial fibrillation in wild-type transthyretin cardiac amyloidosis: a systematic review and clinical experience. *ESC Heart Fail*. 2018;5:772-779.
62. Feng D, Syed IS, Martinez M, Oh JK, Jaffe AS, Grogan M, Edwards WD, Gertz MA, Klarich KW. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. *Circulation*. 2009;12;119(18):2490-2497.
63. Donnellan E, Wazni OM, Saliba WI, et al. Cardiac devices in patients with transthyretin amyloidosis: impact on functional class, left ventricular function, mitral regurgitation, and mortality. *J Cardiovasc Electrophysiol*. 2019;30:2427-2432.
64. Sayed RH, Rogers D, Khan F, et al. A study of implanted cardiac rhythm recorders in advanced cardiac AL amyloidosis. *Eur Heart J*. 2015;36:1098-1105.
65. Varr BC, Zarafshar S, Coakley T, et al. Implantable cardioverter-defibrillator placement in patients with cardiac amyloidosis. *Heart Rhythm* 2014;11:158-162.
66. Sanchorawala V. High-dose melphalan and autologous peripheral blood stem cell transplantation in AL amyloidosis. *Acta Haematol*. 2020;143:381-387.
67. Cordes S, Dispenzieri A, Lacy MQ, et al. Ten-year survival after autologous stem cell transplantation for immunoglobulin light chain amyloidosis. *Cancer* 2012;118:6105-6109.
68. Reece DE, Hegenbart U, Sanchorawala V, et al. Long-term follow-up from a phase 1/2 study of single-agent bortezomib in relapsed systemic AL amyloidosis. *Blood* 2014;124:2498-2506.
69. Abeykoon JP, Zanwar S, Dispenzieri A, et al. Daratumumab-based therapy in patients with heavily-pretreated AL amyloidosis. *Leukemia* 2019;33:531-536.
70. Palladini G, Kastritis E, Maurer MS, et al. Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA. *N Engl J Med*. 2021;385:46-58.
71. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379:1007-1016.
72. Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. *Stat Med*. 1999;18:1341-1354.
73. Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. *Neurology* 2012;79:785-792.
74. Judge DP, Heitner SB, Falk RH, et al. Transthyretin stabilization by AG10 in symptomatic transthyretin amyloid cardiomyopathy. *J Am Coll Cardiol*. 2019;74:285-295.
75. Castano A, Helmke S, Alvarez J, Delisle S, Maurer MS. Diflunisal for ATTR cardiac amyloidosis. *Congest Heart Fail*. 2012;18:315-319.
76. Ikram A, Donnelly JP, Sperry BW, Samaras C, Valent J, Hanna M. Diflunisal tolerability in transthyretin cardiac amyloidosis: a single center's experience. *Amyloid* 2018;25:197-202.


BUY NOW

Because learning changes everything.®

mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.

Mc Graw Hill

FUSTER & HURST'S THE HEART 15TH EDITION



77. Rosenblum H, Castano A, Alvarez J, Goldsmith J, Helmke S, Maurer MS. TTR (Transthyretin) stabilizers are associated with improved survival in patients with TTR cardiac amyloidosis. *Circ Heart Fail.* 2018;11:e004769.
78. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med.* 2018;379:11-21.
79. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med.* 2018;379:22-31.
80. Minamisawa M, Claggett B, Adams D, et al. Association of patisiran, an RNA Interference therapeutic, with regional left ventricular myocardial strain in hereditary transthyretin amyloidosis: the APOLLO study. *JAMA Cardiol.* 2019;4:466-472.
81. Solomon SD, Adams D, Kristen A, et al. Effects of patisiran, an RNA interference therapeutic, on cardiac parameters in patients with hereditary transthyretin-mediated amyloidosis. *Circulation* 2019;139:431-443.
82. Benson MD, Dasgupta NR, Rissing SM, Smith J, Feigenbaum H. Safety and efficacy of a TTR specific antisense oligonucleotide in patients with transthyretin amyloid cardiomyopathy. *Amyloid* 2017;24:219-225.
83. Dasgupta NR, Rissing SM, Smith J, Jung J, Benson MD. Inotersen therapy of transthyretin amyloid cardiomyopathy. *Amyloid* 2020;27:52-58.
84. Obici L, Cortese A, Lozza A, et al. Doxycycline plus tauroursodeoxycholic acid for transthyretin amyloidosis: a phase II study. *Amyloid* 2012;19 Suppl 1:34-36.
85. Wixner J, Pilebro B, Lundgren HE, Olsson M, Anan I. Effect of doxycycline and ursodeoxycholic acid on transthyretin amyloidosis. *Amyloid* 2017;24:78-79.
86. Higaki JN, Chakrabartty A, Galant NJ, et al. Novel conformation-specific monoclonal antibodies against amyloidogenic forms of transthyretin. *Amyloid* 2016;23:86-97.
87. Swiecicki PL, Edwards BS, Kushwaha SS, Dispenzieri A, Park SJ, Gertz MA. Left ventricular device implantation for advanced cardiac amyloidosis. *J Heart Lung Transplant* 2013;32:563-568.
88. Kittleson MM, Cole RM, Patel J, et al. Mechanical circulatory support for cardiac amyloidosis. *Clin Transplant* 2019;33:e13663.
89. Barrett CD, Alexander KM, Zhao H, et al. Outcomes in patients with cardiac amyloidosis undergoing heart transplantation. *JACC Heart Fail.* 2020;8:461-468.
90. Chen Q, Moriguchi J, Levine R, et al. Outcomes of heart transplantation in cardiac amyloidosis patients: a single center experience. *Transplant Proc.* 2020;53(1):329-334.
91. Carvalho A, Rocha A, Lobato L. Liver transplantation in transthyretin amyloidosis: issues and challenges. *Liver Transpl.* 2015;21:282-292.
92. Nelson LM, Penninga L, Villadsen GE, et al. Outcome in patients treated with isolated liver transplantation for familial transthyretin amyloidosis to prevent cardiomyopathy. *Clin Transplant* 2015;29:1098-1104.
93. Damy T, Kristen AV, Suhr OB, et al. Transthyretin cardiac amyloidosis in continental Western Europe: an insight through the Transthyretin Amyloidosis Outcomes Survey (THAOS). *Eur Heart J.* 2019;1;ehz173.
94. Seferovic PM, Ponikowski P, Anker SD, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2019;21:1169-1186.

BUY NOW

Because learning changes everything.®

mhprofessional.com

817103346 – ©2022 McGraw Hill LLC. All Rights Reserved.