Curr Cardiol Rep (2017) 19: 97
DOI 10.1007/s11886-017-0911-5



# Transthyretin Cardiac Amyloidosis

**Anit K. Mankad**[1] · **Keyur B. Shah**[2]

Published online: 24 August 2017


**Abstract**
*Purpose of Review* Transthyretin (TTR)-related cardiac amyloidosis is a progressive infiltrative cardiomyopathy that mimics hypertensive, hypertrophic heart disease and may go undiagnosed. Transthyretin-derived amyloidosis accounts for 18% of all cases of cardiac amyloidosis. Thus, the study's purpose is to provide a comprehensive review of transthyretin cardiac amyloidosis.
*Recent Findings* Wild-type transthyretin (ATTRwt) protein causes cardiac amyloidosis sporadically, with 25 to 36% of the population older than 80 years of age are at risk to develop a slowly progressive, infiltrative amyloid cardiomyopathy secondary to ATTRwt. In contrast, hereditary amyloidosis (ATTRm) is an autosomal dominant inherited disease associated with more than 100 point mutations in the transthyretin gene and has a tendency to affect the heart and nervous system. Up to 4% of African-Americans carry the Val122Ile mutation in the transthyretin gene, the most prevalent cause of hereditary cardiac amyloidosis in the USA.
*Summary* Identifying transthyretin cardiac amyloidosis requires increased awareness of the prevalence, signs and symptoms, and diagnostic tools available for discrimination of this progressive form of cardiomyopathy associated with left ventricular hypertrophy. While there are no FDA-approved medical treatments, investigation is underway on agents to reduce circulating mutated transthyretin.

**Keywords** Heart failure · Cardiac amyloidosis · Transthyretin · Restrictive cardiomyopathy · Hereditary amyloidosis

This article is part of the Topical Collection on *Myocardial Disease*

✉ Anit K. Mankad
anit.mankad@va.gov

[1] Division of Cardiology, Hunter Holmes McGuire Veterans Affairs Medical Center, Richmond, VA, USA

[2] The Pauley Heart Center, Virginia Commonwealth University, Richmond, VA, USA

## Introduction

Amyloid deposits form from the misfolding of endogenous proteins into an insoluble beta-pleated sheet conformation which is resistant to breakdown. Amyloidosis is the syndrome developed as the deposits disrupt normal organ function. While many proteins have been identified as being amyloidogenic, five cause cardiac amyloidosis: immunoglobulin light chain (primary amyloidosis, AL), immunoglobulin heavy chain, transthyretin (ATTR), serum amyloid A, and apolipoprotein A I [1].

Two types of cardiac amyloidosis arise from TTR, a tetrameric protein synthesized primarily in the liver. Individual monomers of the TTR protein can unfold, misfold, and then aggregate to produce amyloid. Wild-type (formally known as senile) amyloidosis arises from genetically unaltered TTR (ATTRwt) and leads to cardiac amyloid deposition in patients usually after their sixth decade of life [2].

Point mutations within the TTR protein alter kinetics for dissociation and thus promote amyloid formation [3]. A hereditary amyloidosis that is transmitted in an autosomal dominant pattern can arise with mutation of the TTR genome (ATTRm).

## Clinical Impact of Mutations of the Transthyretin Gene

### Black Americans (Val122Ile)

In the USA, ATTRm disproportionately affects Black Americans, with several reports associating a race-specific TTR variant with congestive heart failure and high frequency of this mutation observed in Black Americans (~ 1:29) [4, 5, 6••, 7]. Amyloidosis of this variant arises from a point mutation in the TTR gene resulting in a substitution of isoleucine for valine at position 122 (Val122Ile) [8, 9]. Similar to the senile amyloidosis, the Val122Ile mutation results in a clinically significant amyloid deposition that is predominantly isolated to the heart. Compared to Black Americans presenting with AL amyloidosis, ATTRm patients with the Val122Ile mutation are older, have less severe symptoms despite having greater ventricular hypertrophy, lower left ventricular ejection fractions, and greater atrial dilation on echocardiography [10]. Evaluation of living patients has revealed that the mutation is highly prevalent in Black Americans, with 3.43% carrying the Val122Ile mutation [6••]. When evaluating Black patients with clinical heart failure, the prevalence of the mutation is even higher. The Beta-Blocker Evaluation in Survival Trial (BEST) studied the effect of bucindolol in a clinical trial population with symptomatic systolic heart failure, and cardiac amyloidosis was an exclusion. However, of the 207 Black Americans enrolled in the trial, the Val122Ile mutation was detected in 6.3% of patients and in 10% in those greater than 60 years of age [11]. Caucasian variant mutations of the transthyretin gene that have predominantly cardiac manifestations are rare in the USA and include Thr60Ala (Appalachian and Irish regions), Leu111Met (Denmark), and Ile68Leu (Italy) [12].

### Variant Transthyretin Mutations, Neuropathic Syndromes

While the Val122Ile mutation leads to an isolated cardiomyopathy, mutations of the TTR gene endemic to regions of Europe and Asia may lead to cardiac involvement along with familial amyloid polyneuropathy (FAP), which signifies the syndrome of arthropathy, nervous system, and muscular involvement of amyloidosis. These patients can present with varying degrees of neuro-muscular symptoms. There is potential for advanced muscle atrophy, and loss of sensation in the joints can result in destructive Charcot-like arthropathy. These ailments can mask coexistent cardiac involvement, owing to debilitating paresis and impaired nociception [13]. This progressive sensorimotor neuropathy accounts for manifestations from most of the known mutations of the transthyretin gene, and disease progression varies by mutation [14]. The most common mutation to cause FAP is Val30Met (methionine replacing valine at amino acid 30), most often found in Japan, Sweden, and Portugal. Often identified in the third to fifth decade of life, there is severely disabling consequences, with survival limited to 10 years [15•].

## Clinical Presentation

### Heart Failure

Early disease with ATTRm may be minimally symptomatic, especially compared to AL amyloidosis. Patients may complain of mild exercise intolerance or manifest arrhythmias. Clinical and imaging findings may be attributed to other causes of left ventricular hypertrophy and delay diagnosis, while more extensive deposition can mimic hypertrophic cardiomyopathy [16]. Some patients may be asymptomatic initially; however, progressive signs and symptoms of heart failure are common. These include progressive fatigue, reduced activity tolerance, and breathlessness upon exertion. Signs of right heart failure often include hepatomegaly, abdominal fullness, profound peripheral edema, and elevated jugular venous distension [17]. Weight loss is also common and may be secondary to cardiac cachexia or the systemic effects of the disease [18]. With progression of the disease comes congestive heart failure with reduced ejection fraction, predominantly being associated with the cause of early death [19]. Figure 1 reprises micro- and macroscopic pathological changes with their clinical manifestations.

It is well established that light chains from those affected by AL amyloidosis have direct toxicity toward myocytes [20, 21]. Mutant transthyretin fibrils have also been shown to cause oxidative damage to myocyte by triggering NF-kB activation and a pro-inflammatory cascade, altering calcium metabolism and downregulating proteosomal activity [22]. Patients with amyloidosis caused by transthyretin protein may have abundant myocardial infiltration but suffer milder heart failure with prolonged survival [18]. Wild-type systemic amyloidosis is characterized by a slowly progressive heart failure and with greater myocardial infiltration of transthyretin. Despite the greater infiltration, the disease has a median survival of 75 months [23]. Patients with hereditary cardiac amyloidosis have a median survival of 24 to 66 months, compared to 8 months for AL [24]. The longer survival associated with ATTR cardiac amyloidosis further emphasizes the more toxic effect of circulating light chain protein to the myocardial tissue in AL amyloidosis [20].

### Angina

Angina pectoris is not uncommon in cardiac amyloidosis [15•]. Microvascular angina is the result of progressive obstruction of the small intramural coronary arteries by

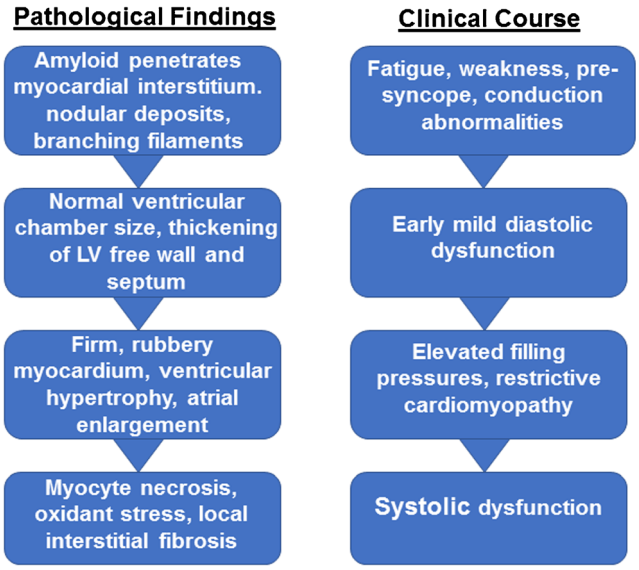


**Fig. 1** Clinicopathological findings in cardiac amyloidosis

amyloid fibril deposition within their walls [25–27]. Acute coronary syndromes including unstable angina and myocardial infarction occurred in 60% of patients with AL in one study and all had normal epicardial coronary arteries during angiography [25]. Patients may also have abnormal findings on exercise stress test [25, 28]. Initially, the amyloid fibrils deposit in the vascular wall and involve mostly the media. As the disease progresses, it infiltrates the adventitia and intima, and can result in complete obliteration of microcirculation vessels [19]. On coronary angiography, these patients typically have minimal epicardial coronary artery disease but can have abnormal flow reserve at the level of the microcirculation [19–21].

## Arrhythmias

The conduction system of the heart, including the sinus node, atrioventricular node, and His bundle, are not spared and disturbances are frequently described with cardiac amyloidosis [29–31]. Involvement of the sinus node is common and can result in significant bradyarrhythmias contributing to sudden cardiac death in patients with AL amyloidosis [30]. Patients given implantable loop recorders showed marked bradycardia caused by complete atrioventricular block as the initial rhythm change detected most frequently just before cardiac arrest [32].

Dysrhythmias, in particular from atrial origin, can often be associated with cardiac amyloidosis. Atrial arrhythmias are frequent and symptomatic arrhythmias, and may need to be addressed with pharmacological or ablative therapies. Atrial fibrillation is observed more often in ATTRwt (30%) as compared to ATTRm (10%), while the incidence is 20% in AL amyloid [33]. Of importance, patients with atrial fibrillation or atrial standstill should receive anticoagulation as the risk for intracardiac thrombus, and thromboembolism is markedly increased [34, 35].

The indications for pacemaker implantation in cardiac amyloidosis are essentially similar to those in the general population [36]. As discussed above, patients with amyloid cardiomyopathy may be heart rate dependent in the face of autonomic neuropathy, hypoalbuminemia, and fixed ventricular stroke volume, and a lower threshold for pacemaker is often considered [37, 38]. Only 3.9% of patients with cardiac amyloidosis have been reported to require a pacemaker for complete heart block, isolated sinus node dysfunction, sinoatrial, atrioventricular, or His-Purkinje disease [39]. An older case series of 16 consecutive subjects with the ATTRm Val30Met variant amyloidosis suggested higher rates of pacemaker requirement, of which five required pacemaker implantation within 14 months of being followed (three for symptomatic complete heart block, one with second-degree heart block, one with symptomatic sinus node dysfunction) [40]. There is no current evidence of survival benefit of pacemakers in cardiac amyloidosis [39, 41].

The benefit of an implantable cardioverter defibrillator (ICD) or cardiac resynchronization is undefined. Unexplained syncope is a powerful prognostic indicator [37]. Pulseless electrical activity has been found to be the cause of sudden death in a disproportional number of patients with cardiac amyloidosis [36]. A study that elucidated the impact of implantable cardioverter defibrillator in cardiac amyloidosis patients found that mortality is mainly due to electromechanical dissociation not amendable to ICD treatments [38]. Ventricular tachyarrhythmias that required ICD therapies were observed in only 19% of patients; however, 80% of those patients had successful termination of life-threatening ventricular arrhythmias [42], while another study showed appropriate ICD discharges occurred almost exclusively in patients with AL type [43]. Despite subset of studies showing benefits of ICD therapies in terminating fatal ventricular arrhythmias, there are currently no randomized clinical trials to date showing survival benefits of ICD implantation in cardiac amyloidosis [40]. The general recommendations for ICD treatment remain a controversial topic and more research is needed.

## Prognosis

The survival in ATTRm is considerably better than AL cardiac amyloidosis (median 27 vs 5 months) [10]. In contrast, data on outcomes of Black Americans with TTR cardiac amyloidosis compared to Caucasian with wild-type TTR amyloidosis, a phenotypically similar condition, reveal that Black Americans present with more advanced disease. Compared to ATTRwt, Val122Ile patients in a small multicenter prospective study had higher rates of cardiovascular

hospitalization (64 vs 28%) and decreased survival (73 vs 22% died, median survival 26 vs 43 months) [44]. This differs with survival data for European variant mutations causing cardiac amyloidosis: Thr60Ala (41 months) and Leu111Met (12–36 months) [45, 46].

## Diagnosis

### Electrocardiography

A marker for heightened consideration of cardiac amyloidosis includes having a low voltage on electrocardiogram (ECG) despite increased left ventricular wall thickness on echocardiographic images. Amyloid infiltration dampens the QRS complexes on surface electrocardiography; therefore, reduced voltage on the ECG relative to the left ventricular mass should heighten consideration of cardiac amyloidosis. Measuring the ratio of ECG voltage to the left ventricular cross-sectional area improves the sensitivity and specificity for assessing cardiac amyloid infiltration to greater than 80% [47, 48, 49]. When compared to AL amyloidosis (46–60%), ATTR typically has reduced rates of low voltage (25–40%) [33]. While less prevalent in ATTRm, and in contradistinction to ATTRwt, low voltage has been shown to correlate with pathogenesis of ATTRm cardiac amyloidosis independent of gender, age, and left ventricular wall thickness [50]. Atrial fibrillation is observed more often in ATTRwt (30%) as compared to ATTRm (10%), while the incidence is 20% in AL amyloid [33]. Carrying a Val122Ile mutation is associated with an increased appearance of premature atrial contractions and Q waves when compared to subjects without the mutated allele [51], which brings to discussion another common ECG finding known as the pseudo-infarction pattern (Fig. 2), typically observed in the inferior and septal leads and without coexistent coronary artery disease and equally observed in AL and ATTR amyloidosis [33]. As amyloid deposits progressively replace conducting myocardium, the patient may develop Q waves on the surface ECG typically found in the inferior and septal leads in the absence of epicardial coronary disease; it is equally observed in AL and ATTR amyloidoses [33]. The prevalence of this "pseudo-infarction" pattern or poor R wave progression is increased as amyloid deposition becomes more diffuse [52].

### Echocardiography

The first description of echocardiographic features specific to cardiac amyloid was described by Child et al. in 1976 [53]. This case series presented findings of symmetrically increased left ventricular wall thickness in the absence of hypertension or aortic valve disease, decreased systolic thickening of the interventricular septum and left ventricular posterior wall, and small to normal size of the left ventricular cavity. Also discussed was an associated finding of pericardial effusion. A decade later, Falk et al. assessed the now common reference to a "speckled" appearance to the left ventricular wall (Fig. 3), due to increased myocardial echogenicity, shown to have a sensitivity of 87% and a specificity of 81% using now outdated echocardiogram technology [48]. When including atrial septal thickening, the specificity was increased to 100%. Degree of left ventricular wall thickness and left ventricular ejection fraction were both inversely correlated with survival [54]. In this report, of subjects with a mean wall thickness between 12 and 15 mm, 48% had granular sparkling, 41% had left atrial enlargement, and 52% had clinical heart failure. Once the mean thickness was greater than 15 mm, 72% had granular sparkling, 83% had left atrial enlargement, and 80% had evidence of heart failure.

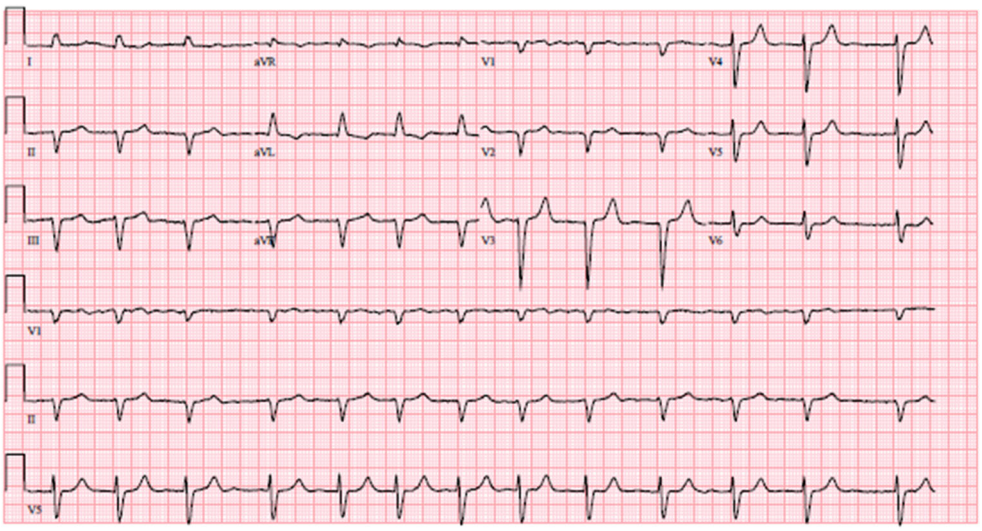


**Fig. 2** Pseudo-infarction pattern of cardiac amyloidosis on electrocardiogram

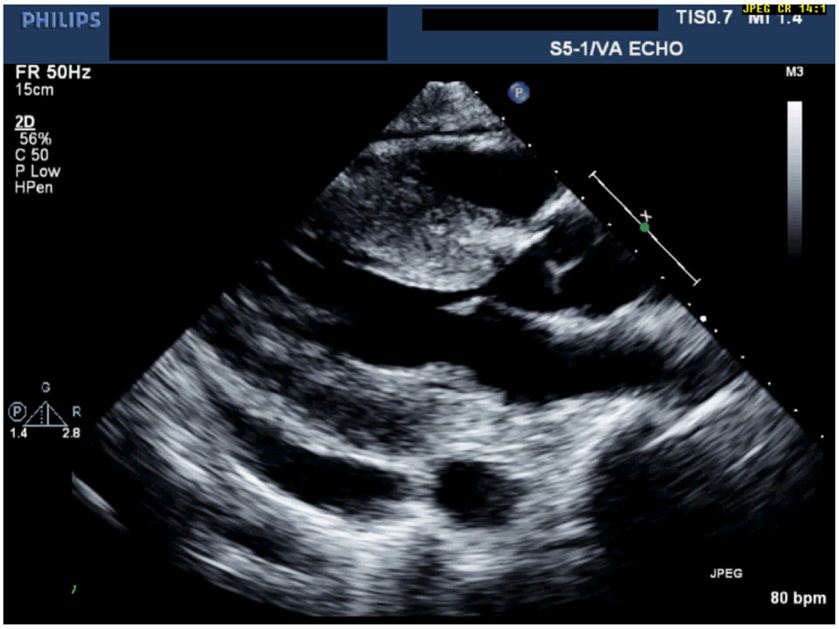


**Fig. 3** Echocardiographic findings in cardiac amyloidosis. Notable left ventricular hypertrophy with classic "speckled" pattern of myocardial echogenicity. A pericardial effusion is often visualized

Contemporary studies have delineated differences on two-dimensional echocardiography among the subtypes of cardiac amyloidosis [7]. In an Italian study, Rapezzi and colleagues studied 233 subjects divided into AL, ATTRwt, and ATTRm [50]. Wall thickness (and by theory infiltration by fibrils) was lowest, and overall, the most blunted echocardiographic findings were in the AL group, despite this group having the worst survival, again suggesting the effect of the greater burden of direct toxicity of light chain infiltration. Left ventricular ejection fraction was lowest in the ATTRwt group while findings of atrial septal thickening and pericardial effusion were no different among the three groups.

Strain (myocardial deformation) is a measure of the difference in velocity between two Doppler points in the same plane (speckle tracking technology), best measured in the longitudinal plane (longitudinal strain). This measure has had tremendous impact in its ability to measure subtle myocardial dysfunction, separating active contraction from passive translational motion such as tethering that limits standard tissue Doppler [7]. Newer technology has allowed specific measures of regional strain of the base, middle, and apex of the left ventricle, as well as the temporal intensity of the change in deformation (strain rate). When compared to subjects with non-cardiac AL amyloid, those with infiltration of the left ventricle (mean wall thickness of greater than 12 mm) have significantly reduced systolic and diastolic longitudinal strain and strain rate (base and mid-ventricle), while tissue Doppler could not separate these groups [55]. This relationship was observed to a greater degree in subjects with cardiac amyloid and a history of congestive heart failure. Tissue Doppler was felt to be suboptimal due to greater passive translational motion of the base of the ventricle, making strain a more sensitive measure of myocardial dysfunction (before the onset of heart failure). Strain imaging was least effective in distinguishing groups in the anterior wall and apex (apical sparing in longitudinal strain has been found to be a unique finding in cardiac amyloidosis reproduced also in cardiac magnetic resonance imaging) [56]. In addition to longitudinal strain, cardiac amyloidosis is associated with severely reduced strain measured in the radial and circumferential aspects, when compared to hypertrophic cardiomyopathy and secondary left ventricular hypertrophy [57]. It is noteworthy that the cardiac amyloidosis group in this study was in an advanced stage, with a mean left ventricular ejection fraction of 39%. Interestingly, anterior wall longitudinal strain was less effective in differentiating cardiac amyloid from hypertrophic cardiomyopathy (despite the higher mean ejection fraction of 57%), again showing reduced performance of strain imaging of this wall.

These earlier studies led to the most comprehensive and current evaluation combining work by Koyama and Sun in strain imaging with that of Rapezzi in TTR amyloid assessment, also led by Rodney Falk's group [49]. One hundred seventy-two subjects were likewise divided into three groups (AL, ATTRm, ATTRwt). The total cohort had reduced global longitudinal and radial strain, left atrial enlargement, increased wall thickness with preserved ejection fraction, and increased pulmonary pressures, and half had a pericardial effusion. Longitudinal strain was least impaired in ATTRm (−15 ± 4%) than ATTRwt (−12 ± 4%) and AL (−11 ± 3%, $p < 0.001$). Once again, ATTRwt (vs ATTRm vs AL) had the thickest walls (mean thickness 17 ± 2 vs 15 ± 2 vs 15 ± 2 mm, $p < 0.001$) and also had the most reduced functional

assessment by ejection fraction and cardiac output. Similar to previously described, despite severe abnormalities in basal and mid-ventricular strain, apical longitudinal strain was preserved regardless of the etiology. Doppler assessment of diastolic dysfunction, interatrial septal thickness, and presence of pericardial effusion did not significantly differ between groups.

### Biomarkers

Cardiac troponin, as a marker of myocardial cell death, and B-type natriuretic peptide (BNP), as a sensitive marker of myocardial dysfunction, have been shown to have prognostic significance in AL amyloid [58, 59]. Review of limited data show elevated B-type natriuretic peptide levels in ATTRm, with a reduced rate of troponin elevation [60]. Suhr and colleagues assessed 29 subjects with Val30Met variant ATTR and found that BNP was elevated above normal in 76% and correlated with ventricular septal wall thickness, left atrial diameter, and basal septal strain [60]. As a predictor of echocardiographic involvement of the heart, BNP had a sensitivity of 93% and a specificity of 40% with a negative predictive value of 86%, on par with basal septal strain echocardiographic imaging (sensitivity of 81%, specificity of 36%, and negative predictive value of 50%). The authors of this trial discussed the potential use utility of BNP as a marker of deterioration. While there are no significant differences in BNP levels among those affected by AL and ATTRm cardiac amyloidosis [10], troponin concentrations are higher in AL cardiac amyloidosis. This discrepancy again highlights the potential direct toxicity by free light chain fibrils in AL amyloid and rather a mechanical stress provided by the ATTR fibrils. Emerging data suggests a prognostic role of troponin for ATTR [61, 62].

### Cardiac Magnetic Resonance

Cardiac magnetic resonance (CMR) imaging has become a valuable tool in assessing for cardiac amyloid infiltration [7]. Tissue characterization specifically with late gadolinium enhancement imaging has been reported to be one of the most accurate predictors of endomyocardial biopsy-positive amyloidosis [63]. Enhancement patterns on late gadolinium images has been described as either diffuse, circumferential subendocardial, or patchy focal [52]. Left ventricular mass was significantly larger, and late gadolinium enhancement was substantially more extensive in ATTR than in AL [64]. Subendocardial enhancement was more common in AL cardiac amyloidosis. Right ventricular gadolinium enhancement was apparent in 100% of ATTR patients compared with 72% of AL. Apical sparing in longitudinal strain, as discussed in echocardiography, is a unique finding and has been reproduced in CMR imaging [56].

Early darkening of the blood pool after contrast, due to rapid washout of gadolinium into an enlarged subendocardial interstitial space, can be quantitatively assessed by mapping of T1 kinetics of the blood pool and subendocardium early after gadolinium administration. White et al. published a study in CMR to assess prognosis in cardiac amyloidosis [65]. They employed the observation that in contradistinction to normal myocardium which crosses the null point (becomes black) *after* the blood pool, in cardiac amyloidosis, there is "failure to null the myocardium" represented as greater than 50% of myocardial tissue becoming black at an earlier inversion time as compared to blood.

### Nuclear Imaging

$^{99m}$Technetium pyrophosphate ($^{99m}$Tc-PYP) or $^{99m}$technetium-3,3-diphosphono-1,2-propanodicarboxylic acid ($^{99m}$Tc-DPD) scintigraphy, conventional bone tracers, bind to TTR amyloid deposits and are very helpful for diagnosing ATTR cardiac amyloidosis. Subjects with ATTR have significantly higher semi-quantitative cardiac visual score (uptake of tracer in heart compared to bone and a higher heart to contralateral lung $^{99m}$Tc-PYP uptake ratio ($\geq$ 1.5 was identified ATTR cardiac amyloidosis with 97% sensitivity and 100% specificity) [66]. The use of 99mTc-DPD scintigraphy (not approved in the USA) has been even more exhaustively studied and has proven to also be useful for identifying myocardial infiltration of ATTR across a wide spectrum of patients [67].

### Histopathology

Tissue confirmation of amyloid deposition is considered the gold standard for confirmation of the diagnosis of amyloidosis. Cardiac deposition of amyloid is diffuse and homogenous in its distribution, allowing for an essentially 100% sensitivity when obtaining a pathological diagnosis [68]. Because amyloidosis is a systemic disease, multiple sources can provide a diagnosis, but the yield can vary greatly from organ to organ. Fat pad biopsy has had sensitivities 78–93% to detect AL amyloid; other sites for consideration include rectal mucosa (sensitivity of 84%) as well as kidney/liver/carpal tunnel biopsies (sensitivities around 90%) [69, 70, 71]. Endomyocardial biopsy from the right ventricular septum has a sensitivity up to 100% [72]. Fine et al. published the largest study in ATTR and fat pad aspiration to date (including 286 subjects) comparing the yield of cardiac and non-cardiac biopsies in patients with ATTRwt and ATTRm [73]. The yield for ATTRm in abdominal fat pad aspiration (67% of 141 specimens) far exceeded that for ATTRwt (14% of 84 specimens), but only 18 patients (11% of those with genotype data) had the Val122Ile mutation. Fat pad aspiration was less sensitive than endomyocardial biopsy (100% of 42 ATTRm and 89

ATTRwt specimens). The highest yield for ATTRm for non-cardiac biopsies came from rectal (81% of 52 specimens) and sural nerve (83% of 54 specimens) biopsies.

Congo red stain is routine; however, implementing fluorescent microscopy improves sensitivity for amyloid deposits [74]. More specific techniques of identifying the subtype of amyloid fibrils include immunohistochemical staining. Biopsy specimens can be stained for antibodies to kappa- or lambda-free light chains to differentiate AL amyloid and further be stained for antibodies to transthyretin amyloid for TTR. While valid for amyloid typing, there are considerable pitfalls to this technique including failure to react to truncated AL light chains, and a number of hereditary amyloidoses will be missed by a limited antibody panel [75].

Finally, mass spectrometry can be performed to examine the affected tissue and study the protein constituents of the amyloid fibril [76]. Formalin-fixed or formalin-unfixed biopsy specimens are subjected to direct chemical analysis using bioinformatic software rather than antibodies. Inclusion of laser microdissection of the fibrils followed by tandem mass spectrometry can generate a nearly complete protein composition of the amyloid fibril and has been shown to have a specificity of 100% and sensitivity of 98% [77].

### Genetic Testing

There are over 100 polymorphisms encoding the variant gene that transcripts the transport protein transthyretin, located on the long (q) arm of chromosome 18 at position 12.1 (18q12.1), with 80 confirmed pathogenic mutations [78]. Isoelectric focusing gel electrophoresis, a method of separating molecules by their isoelectric point (pI) and pH, can differentiate ATTRwt from greater than 95% of variants of ATTRm [33]. Among those with ATTRwt, only one protein band is visualized, while heterozygous ATTRm will show both the wild-type TTR at the typical pI and a second mutant TTR (two distinct protein bands). A single protein band at this pI would suggest homozygosity for the Ile122 mutation. Conclusive genetic distinction between ATTRm and ATTRwt is obtained from polymerase chain reaction amplification and DNA sequencing of the transthyretin exons 1 to 4, validating isoelectric focusing [33].

## Therapeutic Options

The clinical management of a patient with symptomatic restrictive amyloid is focused around managing fluid balance; hence, the mainstays of therapy are loop diuretics, potentially in combination with thiazide diuretics and aldosterone antagonist [24]. In the setting of renal insufficiency, nephrotic syndrome, and autonomic dysfunction, the management of heart failure can be very challenging and with limiting therapeutic options [79].

Traditional disease-modifying medications for heart failure have no proven role in the treatment of progressive amyloid heart disease [7]. In fact, typical heart failure medications including digitalis, calcium channel blockers, beta-blockers, or angiotensin-converting enzyme inhibitors can have significant adverse effects on amyloid-associated cardiomyopathy [18]. Drugs that slow the heart rate (beta-blockers, calcium channel blockers) are poorly tolerated, as patients with restrictive heart disease often have fixed stroke volumes and the cardiac output is highly dependent on the heart rate [79]. The prevalence of conduction disease is high and administration of these drug could be life threatening. Calcium channel blockers have a negative inotropic potential that outweighs the beneficial effects of left ventricular relaxation or afterload reduction [80]. In addition to worsening symptoms, there are published case reports of sudden death of patients with amyloidosis after administration of such therapies [81, 82]. Digitalis has a high affinity to bind amyloid fibrils, leading to unpredictable and possibly toxic circulating concentrations, prohibiting its use in amyloid heart disease [83, 84]. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and combination vasodilators may be poorly tolerated as orthostatic hypotension is often present at baseline [85]. Inotropes may have a palliative role, but from clinical experience, the reduction in symptomatology and improvement in quality of life are only modest. Patients with pacemakers may derive clinical benefit from increased lower rate limits for pacing.

### Advanced Heart Failure Therapies

Despite the advances in mechanical circulatory support, there are insufficient data to support the use of left ventricular assist devices in amyloid cardiomyopathy and even less data in cardiac amyloidosis [86]. By the nature of the illness, infiltration can limit adequate left ventricular filling and increase the burden of wall suction, thereby reducing the potential for benefit [87]. The 2016 ISHLT listing criteria guidelines recommend that selected patients with TTR cardiac amyloidosis should be considered for combined heart and liver transplantation at experienced centers with established collaboration of cardiology, hematology, and neurology teams (Class IIA, Level of Evidence: B) [88••]. The primary extra-cardiac manifestation to evaluate is neurological deficits, of which liver transplantation has been shown to provide significant improvement 5 years after transplant compared to those not transplanted [89]. It is proposed that younger patients should be considered for dual heart liver transplant, as 5-year outcomes are comparable to heart transplant alone, and the affected liver may be used in a domino sequence for isolated liver transplantation, increasing access to donor allografts [90]. Older patients with limited non-cardiac involvement may also be considered for

isolated heart transplantation, as the slow amyloid disease process is unlikely to influence outcomes in this cohort [88••].

### Amyloid-Specific Therapy

There are no Food and Drug Administration-approved drugs for the treatment of ATTR cardiac amyloidosis. Agents intended to stabilize the TTR tetramer, silence the TTR gene expression and amyloid reabsorbing antibodies are at various stages of investigation.

## Conclusion

Identifying transthyretin cardiac amyloidosis required increased awareness of the prevalence, signs and symptoms, and diagnostic tools available for discrimination of this progressive form of cardiomyopathy associated with left ventricular hypertrophy. Up to 4% of African-Americans carry the Val122Ile mutation in the transthyretin gene, the most prevalent cause of hereditary cardiac amyloidosis in the USA. While there are no FDA-approved medical treatments, advanced stage cardiac amyloidosis may be treated with heart or dual heart and liver transplantation. Investigation is underway on agents to reduce circulating mutated transthyretin.

#### Compliance with Ethical Standards

**Conflict of Interest** Anit K. Mankad reports grants from Covance. Keyur B. Shah reports grants from Alnylam.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance


1. Sipe JD, Benson MD, Buxbaum JN, Ikeda S, Merlini G, Saraiva MJM, et al. Nomenclature 2014: amyloid fibril proteins and clinical classification of the amyloidosis. Amyloid Int J Exp Clin Investig Off J Int Soc Amyloidosis. 2014;21(4):221–4. doi:10.3109/13506129.2014.964858.
2. Cornwell GG, Murdoch WL, Kyle RA, Westermark P, Pitkänen P. Frequency and distribution of senile cardiovascular amyloid. A clinicopathologic correlation. Am J Med. 1983;75(4):618–23.
3. Hammarström P, Jiang X, Hurshman AR, Powers ET, Kelly JW. Sequence-dependent denaturation energetics: a major determinant in amyloid disease diversity. Proc Natl Acad Sci U S A. 2002;99(Suppl 4):16427–32. doi:10.1073/pnas.202495199.
4. Quarta CC, Buxbaum JN, Shah AM, Falk RH, Claggett B, Kitzman DW, et al. The amyloidogenic V122I transthyretin variant in elderly black Americans. N Engl J Med. 2015;372(1):21–9. doi:10.1056/NEJMoa1404852.
5. Buxbaum J, Alexander A, Koziol J, Tagoe C, Fox E, Kitzman D. Significance of the amyloidogenic transthyretin Val 122 Ile allele in African Americans in the Arteriosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) Studies. Am Heart J. 2010;159(5):864–70. doi:10.1016/j.ahj.2010.02.006.
6.•• Jacobson DR, Alexander AA, Tagoe C, Buxbaum JN. Prevalence of the amyloidogenic transthyretin (TTR) V122I allele in 14 333 African-Americans. Amyloid Int J Exp Clin Investig Off J Int Soc Amyloidosis. 2015;22(3):171–4. doi:10.3109/13506129.2015.1051219. **This study revealed the significant prevalence of amyloidogenic transthyretin mutations in the African-American population.**
7. Shah KB, Mankad AK, Castano A, Akinboboye OO, Duncan PB, Fergus IV, et al. Transthyretin cardiac amyloidosis in black Americans. Circ Heart Fail. 2016;9(6):e002558. doi:10.1161/CIRCHEARTFAILURE.115.002558.
8. Gorevic PD, Prelli FC, Wright J, Pras M, Frangione B. Systemic senile amyloidosis. Identification of a new prealbumin (transthyretin) variant in cardiac tissue: immunologic and biochemical similarity to one form of familial amyloidotic polyneuropathy. J Clin Invest. 1989;83(3):836–43. doi:10.1172/JCI113966.
9. Jacobson DR, Gorevic PD, Buxbaum JN. A homozygous transthyretin variant associated with senile systemic amyloidosis: evidence for a late-onset disease of genetic etiology. Am J Hum Genet. 1990;47(1):127–36.
10. Connors LH, Prokaeva T, Lim A, Théberge R, Falk RH, Doros G, et al. Cardiac amyloidosis in African Americans: comparison of clinical and laboratory features of transthyretin V122I amyloidosis and immunoglobulin light chain amyloidosis. Am Heart J. 2009;158(4):607–14. doi:10.1016/j.ahj.2009.08.006.
11. Buxbaum J, Jacobson DR, Tagoe C, Alexander A, Kitzman DW, Greenberg B, et al. Transthyretin V122I in African Americans with congestive heart failure. J Am Coll Cardiol. 2006;47(8):1724–5. doi:10.1016/j.jacc.2006.01.042.
12. Rapezzi C, Quarta CC, Obici L, Perfetto F, Longhi S, Salvi F, et al. Disease profile and differential diagnosis of hereditary transthyretin-related amyloidosis with exclusively cardiac phenotype: an Italian perspective. Eur Heart J. 2013;34(7):520–8. doi:10.1093/eurheartj/ehs123.
13. Benson MD, Cohen AS. Generalized amyloid in a family of Swedish origin. A study of 426 family members in seven generations of a new kinship with neuropathy, nephropathy, and central nervous system involvement. Ann Intern Med. 1977;86(4):419–24.
14. Connors LH, Lim A, Prokaeva T, Roskens VA, Costello CE. Tabulation of human transthyretin (TTR) variants, 2003. Amyloid Int J Exp Clin Investig Off J Int Soc Amyloidosis. 2003;10(3):160–84. doi:10.3109/13506120308998998.
15.• Hanna M. Novel drugs targeting transthyretin amyloidosis. Curr Heart Fail Rep. 2014;11(1):50–7. doi:10.1007/s11897-013-0182-4. **This report is a valuable resource for developmental therapies for transthyretin amyloidosis.**
16. Damy T, Costes B, Hagège AA, Donal E, Eicher J-C, Slama M, et al. Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness. Eur Heart J. 2015; doi:10.1093/eurheartj/ehv583.
17. Arora S, Arora A, Makkar RPS, Monga A. Clinical vistas: stiff heart syndrome. CMAJ Can Med Assoc J. 2003;168(13):1690.
18. Falk RH, Comenzo RL, Skinner M. The systemic amyloidoses. N Engl J Med. 1997;337(13):898–909. doi:10.1056/NEJM199709253371306.
19. Cueto-Garcia L, Reeder GS, Kyle RA, Wood DL, Seward JB, Naessens J, et al. Echocardiographic findings in systemic

amyloidosis: spectrum of cardiac involvement and relation to survival. J Am Coll Cardiol. 1985;6(4):737–43.
20. Liao R, Jain M, Teller P, Connors LH, Ngoy S, Skinner M, et al. Infusion of light chains from patients with cardiac amyloidosis causes diastolic dysfunction in isolated mouse hearts. Circulation. 2001;104(14):1594–7.
21. Brenner DA, Jain M, Pimentel DR, Wang B, Connors LH, Skinner M, et al. Human amyloidogenic light chains directly impair cardiomyocyte function through an increase in cellular oxidant stress. Circ Res. 2004;94(8):1008–10. doi:10.1161/01.RES.0000126569.75419.74.
22. Ton V-K, Mukherjee M, Judge DP. Transthyretin cardiac amyloidosis: pathogenesis, treatments, and emerging role in heart failure with preserved ejection fraction. Clin Med Insights Cardiol. 2015;8(Suppl 1):39–44. doi:10.4137/CMC.S15719.
23. Ng B, Connors LH, Davidoff R, Skinner M, Falk RH. Senile systemic amyloidosis presenting with heart failure: a comparison with light chain–associated amyloidosis. Arch Intern Med. 2005;165(12):1425–9. doi:10.1001/archinte.165.12.1425.
24. Muchtar E, Buadi FK, Dispenzieri A, Gertz MA. Immunoglobulin light-chain amyloidosis: from basics to new developments in diagnosis, prognosis and therapy. Acta Haematol. 2016;135(3):172–90. doi:10.1159/000443200.
25. Mueller PS, Edwards WD, Gertz MA. Symptomatic ischemic heart disease resulting from obstructive intramural coronary amyloidosis. Am J Med. 2000;109(3):181–8.
26. Ishikawa Y, Ishii T, Masuda S, Asuwa N, Kiguchi H, Hirai S, et al. Myocardial ischemia due to vascular systemic amyloidosis: a quantitative analysis of autopsy findings on stenosis of the intramural coronary arteries. Pathol Int. 1996;46(3):189–94.
27. Neben-Wittich MA, Wittich CM, Mueller PS, Larson DR, Gertz MA, Edwards WD. Obstructive intramural coronary amyloidosis and myocardial ischemia are common in primary amyloidosis. Am J Med. 2005;118(11):1287.e1–7. doi:10.1016/j.amjmed.2005.06.017.
28. Dubrey SW, Cha K, Anderson J, Chamarthi B, Reisinger J, Skinner M, et al. The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. QJM Mon J Assoc Physicians. 1998;91(2):141–57.
29. Bharati S, Lev M, Denes P, Modlinger J, Wyndham C, Bauernfeind R, et al. Infiltrative cardiomyopathy with conduction disease and ventricular arrhythmia: electrophysiologic and pathologic correlations. Am J Cardiol. 1980;45(1):163–73.
30. James TN. Pathology of the cardiac conduction system in amyloidosis. Ann Intern Med. 1966;65(1):28–36.
31. Ridolfi RL, Bulkley BH, Hutchins GM. The conduction system in cardiac amyloidosis. Clinical and pathologic features of 23 patients. Am J Med. 1977;62(5):677–86.
32. Sayed RH, Rogers D, Khan F, Wechalekar AD, Lachmann HJ, Fontana M, et al. A study of implanted cardiac rhythm recorders in advanced cardiac AL amyloidosis. Eur Heart J. 2015;36(18):1098–105. doi:10.1093/eurheartj/ehu506.
33. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. Circulation. 2012;126(10):1286–300. doi:10.1161/CIRCULATIONAHA.111.078915.
34. Santarone M, Corrado G, Tagliagambe LM, Manzillo GF, Tadeo G, Spata M, et al. Atrial thrombosis in cardiac amyloidosis: diagnostic contribution of transesophageal echocardiography. J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr. 1999;12(6):533–6.
35. Dubrey S, Pollak A, Skinner M, Falk RH. Atrial thrombi occurring during sinus rhythm in cardiac amyloidosis: evidence for atrial electromechanical dissociation. Br Heart J. 1995;74(5):541–4.
36. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NAM, Freedman RA, American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices), American Association for Thoracic Surgery, Society of Thoracic Surgeons, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;51(21):e1–62. doi:10.1016/j.jacc.2008.02.032.
37. Selvanayagam JB, Hawkins PN, Paul B, Myerson SG, Neubauer S. Evaluation and management of the cardiac amyloidosis. J Am Coll Cardiol. 2007;50(22):2101–10. doi:10.1016/j.jacc.2007.08.028.
38. Roberts WC, Waller BF. Cardiac amyloidosis causing cardiac dysfunction: analysis of 54 necropsy patients. Am J Cardiol. 1983;52(1):137–46.
39. Mathew V, Olson LJ, Gertz MA, Hayes DL. Symptomatic conduction system disease in cardiac amyloidosis. Am J Cardiol. 1997;80(11):1491–2.
40. Eriksson P, Karp K, Bjerle P, Olofsson BO. Disturbances of cardiac rhythm and conduction in familial amyloidosis with polyneuropathy. Br Heart J. 1984;51(6):658–62.
41. Wright JR, Calkins E. Clinical-pathologic differentiation of common amyloid syndromes. Medicine (Baltimore). 1981;60(6):429–48.
42. Varr BC, Zarafshar S, Coakley T, Liedtke M, Lafayette RA, Arai S, et al. Implantable cardioverter-defibrillator placement in patients with cardiac amyloidosis. Heart Rhythm. 2014;11(1):158–62. doi:10.1016/j.hrthm.2013.10.026.
43. Lin G, Dispenzieri A, Kyle R, Grogan M, Brady PA. Implantable cardioverter defibrillators in patients with cardiac amyloidosis. J Cardiovasc Electrophysiol. 2013;24(7):793–8. doi:10.1111/jce.12123.
44. Ruberg FL, Maurer MS, Judge DP, Zeldenrust S, Skinner M, Kim AY, et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). Am Heart J. 2012;164(2):222–228.e1. doi:10.1016/j.ahj.2012.04.015.
45. Sattianayagam PT, Hahn AF, Whelan CJ, Gibbs SDJ, Pinney JH, Stangou AJ, et al. Cardiac phenotype and clinical outcome of familial amyloid polyneuropathy associated with transthyretin alanine 60 variant. Eur Heart J. 2012;33(9):1120–7. doi:10.1093/eurheartj/ehr383.
46. Ranløv I, Alves IL, Ranløv PJ, Husby G, Costa PP, Saraiva MJ. A Danish kindred with familial amyloid cardiomyopathy revisited: identification of a mutant transthyretin-methionine111 variant in serum from patients and carriers. Am J Med. 1992;93(1):3–8.
47. Carroll JD, Gaasch WH, McAdam KP. Amyloid cardiomyopathy: characterization by a distinctive voltage/mass relation. Am J Cardiol. 1982;49(1):9–13.
48. Falk RH, Plehn JF, Deering T, Schick EC, Boinay P, Rubinow A, et al. Sensitivity and specificity of the echocardiographic features of cardiac amyloidosis. Am J Cardiol. 1987;59(5):418–22. doi:10.1016/0002-9149(87)90948-9.
49. Quarta CC, Solomon SD, Uraizee I, Kruger J, Longhi S, Ferlito M, et al. Left ventricular structure and function in transthyretin-related versus light-chain cardiac amyloidosis. Circulation. 2014;129(18):1840–9. doi:10.1161/CIRCULATIONAHA.113.006242.
50. Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. Circulation. 2009;120(13):1203–12. doi:10.1161/CIRCULATIONAHA.108.843334.
51. Jacobson D, Tagoe C, Schwartzbard A, Shah A, Koziol J, Buxbaum J. Relation of clinical, echocardiographic and electrocardiographic features of cardiac amyloidosis to the presence of the transthyretin

V122I allele in older African-American men. Am J Cardiol. 2011;108(3):440–4. doi:10.1016/j.amjcard.2011.03.069.
52. Syed IS, Glockner JF, Feng D, Araoz PA, Martinez MW, Edwards WD, et al. Role of cardiac magnetic resonance imaging in the detection of cardiac amyloidosis. JACC Cardiovasc Imaging. 2010;3(2):155–64. doi:10.1016/j.jcmg.2009.09.023.
53. Child JS, Levisman JA. Echocardiographic manifestations of infiltrative cardiomyopathy. A report of seven cases due to amyloid. Chest. 1977;70(6):726–31. doi:10.1378/chest.70.6.726.
54. Cueto-Garcia L, Reeder GS, Kyle RA, Wood DL, Seward JB, Naessens J, et al. Echocardiographic findings in systemic amyloidosis: spectrum of cardiac involvement and relation to survival. J Am Coll Cardiol. 1985;6(4):737–43.
55. Koyama J, Ray-Sequin PA, Falk RH. Longitudinal myocardial function assessed by tissue velocity, strain, and strain rate tissue Doppler echocardiography in patients with AL (primary) cardiac amyloidosis. Circulation. 2003;107(19):2446–52. doi:10.1161/01.CIR.0000068313.67758.4F.
56. Phelan D, Collier P, Thavendiranathan P, Popović ZB, Hanna M, Plana JC, 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 Br Card Soc. 2012;98(19):1442–8. doi:10.1136/heartjnl-2012-302353.
57. Sun JP, Stewart WJ, Yang XS, Donnell RO, Leon AR, Felner JM, et al. Differentiation of hypertrophic cardiomyopathy and cardiac amyloidosis from other causes of ventricular wall thickening by two-dimensional strain imaging echocardiography. Am J Cardiol. 2009;103(3):411–5. doi:10.1016/j.amjcard.2008.09.102.
58. Dispenzieri A, Kyle RA, Gertz MA, Therneau TM, Miller WL, Chandrasekaran K, et al. Survival in patients with primary systemic amyloidosis and raised serum cardiac troponins. Lancet. 2003;361(9371):1787–9. doi:10.1016/S0140-6736(03)13396-X.
59. Palladini G, Campana C, Klersy C, Balduini A, Vadacca G, Perfetti V, et al. Serum N-terminal pro-brain natriuretic peptide is a sensitive marker of myocardial dysfunction in AL amyloidosis. Circulation. 2003;107(19):2440–5. doi:10.1161/01.CIR.0000068314.02595.B2.
60. Suhr OB, Anan I, Backman C, Karlsson A, Lindqvist P, Mörner S, et al. Do troponin and B-natriuretic peptide detect cardiomyopathy in transthyretin amyloidosis? J Intern Med. 2008;263(3):294–301. doi:10.1111/j.1365-2796.2007.01888.x.
61. Pinney JH, Whelan CJ, Petrie A, Dungu J, Banypersad SM, Sattianayagam P, et al. Senile systemic amyloidosis: clinical features at presentation and outcome. J Am Heart Assoc. 2013;2(2):e000098. doi:10.1161/JAHA.113.000098.
62. Maurer MS, Kristen AV, Rapezzi C, Suhr OB, Kolluri S, Thibaud D. Cardiac biomarkers in patients with transthyretin amyloidosis as documented in THAOS: the transthyretin amyloidosis survey. Presented at ACC13 as a poster abstract,J Am Coll Cardiol. 2013;61(10_S):doi:10.1016/S0735-1097(13)61244-9.
63. Austin BA, Tang WHW, Rodriguez ER, Tan C, Flamm SD, Taylor DO, et al. Delayed hyper-enhancement magnetic resonance imaging provides incremental diagnostic and prognostic utility in suspected cardiac amyloidosis. JACC Cardiovasc Imaging. 2009;2(12):1369–77. doi:10.1016/j.jcmg.2009.08.008.
64. Dungu JN, Valencia O, Pinney JH, Gibbs SDJ, Rowczenio D, Gilbertson JA, et al. CMR-based differentiation of AL and ATTR cardiac amyloidosis. JACC Cardiovasc Imaging. 2014;7(2):133–42. doi:10.1016/j.jcmg.2013.08.015.
65. White JA, Kim HW, Shah D, Fine N, Kim K-Y, Wendell DC, et al. CMR imaging with rapid visual T1 assessment predicts mortality in patients suspected of cardiac amyloidosis. JACC Cardiovasc Imaging. 2014;7(2):143–56. doi:10.1016/j.jcmg.2013.09.019.
66. Bokhari S, Castaño A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. (99m)Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. Circ Cardiovasc Imaging. 2013;6(2):195–201. doi:10.1161/CIRCIMAGING.112.000132.
67. Rapezzi C, Quarta CC, Guidalotti PL, Pettinato C, Fanti S, Leone O, et al. Role of (99m)Tc-DPD scintigraphy in diagnosis and prognosis of hereditary transthyretin-related cardiac amyloidosis. JACC Cardiovasc Imaging. 2011;4(6):659–70. doi:10.1016/j.jcmg.2011.03.016.
68. Gertz MA, Grogan M, Kyle RA, Tajik AJ. Endomyocardial biopsy-proven light chain amyloidosis (AL) without echocardiographic features of infiltrative cardiomyopathy. Am J Cardiol. 1997;80(1):93–5.
69. Dhingra S, Krishnani N, Kumari N, Pandey R. Evaluation of abdominal fat pad aspiration cytology and grading for detection in systemic amyloidosis. Acta Cytol. 2007;51(6):860–4.
70. van Gameren II, Hazenberg BPC, Bijzet J, van Rijswijk MH. Diagnostic accuracy of subcutaneous abdominal fat tissue aspiration for detecting systemic amyloidosis and its utility in clinical practice. Arthritis Rheum. 2006;54(6):2015–21. doi:10.1002/art.21902.
71. Kyle RA, Bayrd ED. Amyloidosis: review of 236 cases. Medicine (Baltimore). 1975;54(4):271–99.
72. Ardehali H, Qasim A, Cappola T, Howard D, Hruban R, Hare JM, et al. Endomyocardial biopsy plays a role in diagnosing patients with unexplained cardiomyopathy. Am Heart J. 2004;147(5):919–23. doi:10.1016/j.ahj.2003.09.020.
73. Fine NM, Arruda-Olson AM, Dispenzieri A, Zeldenrust SR, Gertz MA, Kyle RA, et al. Yield of noncardiac biopsy for the diagnosis of transthyretin cardiac amyloidosis. Am J Cardiol. 2014;113(10):1723–7. doi:10.1016/j.amjcard.2014.02.030.
74. Linke RP. Highly sensitive diagnosis of amyloid and various amyloid syndromes using Congo red fluorescence. Virchows Arch Int J Pathol. 2000;436(5):439–48.
75. Picken MM. Amyloidosis—where are we now and where are we heading? Arch Pathol Lab Med. 2010;134(4):545–51. doi:10.1043/1543-2165-134.4.545.
76. Lavatelli F, Vrana JA. Proteomic typing of amyloid deposits in systemic amyloidoses. Amyloid Int J Exp Clin Investig Off J Int Soc Amyloidosis. 2011;18(4):177–82. doi:10.3109/13506129.2011.630762.
77. Vrana JA, Gamez JD, Madden BJ, Theis JD, Bergen HR, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. Blood. 2009;114(24):4957–9. doi:10.1182/blood-2009-07-230722.
78. Benson MD, Kincaid JC. The molecular biology and clinical features of amyloid neuropathy. Muscle Nerve. 2007;36(4):411–23. doi:10.1002/mus.20821.
79. Grogan M, Dispenzieri A. Natural history and therapy of AL cardiac amyloidosis. Heart Fail Rev. 2015;20(2):155–62. doi:10.1007/s10741-014-9464-5.
80. Griffiths BE, Hughes P, Dowdle R, Stephens MR. Cardiac amyloidosis with asymmetrical septal hypertrophy and deterioration after nifedipine. Thorax. 1982;37(9):711–2.
81. Pollak A, Falk RH. Left ventricular systolic dysfunction precipitated by verapamil in cardiac amyloidosis. Chest. 1993;104(2):618–20.
82. Gertz MA, Falk RH, Skinner M, Cohen AS, Kyle RA. Worsening of congestive heart failure in amyloid heart disease treated by calcium channel-blocking agents. Am J Cardiol. 1985;55(13 Pt 1):1645.
83. Cassidy JT. Cardiac amyloidosis. Two cases with digitalis sensitivity. Ann Intern Med. 1961;55:989–94.
84. Rubinow A, Skinner M, Cohen AS. Digoxin sensitivity in amyloid cardiomyopathy. Circulation. 1981;63(6):1285–8.
85. Falk RH. Cardiac amyloidosis: a treatable disease, often overlooked. Circulation. 2011;124(9):1079–85. doi:10.1161/CIRCULATIONAHA.110.010447.

86. Swiecicki PL, Edwards BS, Kushwaha SS, Dispenzieri A, Park SJ, Gertz MA. Left ventricular device implantation for advanced cardiac amyloidosis. J Heart Lung Transplant Off Publ Int Soc Heart Transplant. 2013;32(5):563–8. doi:10.1016/j.healun.2013.01.987.
87. Siegenthaler MP, Martin J, van de Loo A, Doenst T, Bothe W, Beyersdorf F. Implantation of the permanent Jarvik-2000 left ventricular assist device: a single-center experience. J Am Coll Cardiol. 2002;39(11):1764–72.
88.•• Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, International Society for Heart Lung Transplantation (ISHLT) Infectious Diseases Council, International Society for Heart Lung Transplantation (ISHLT) Pediatric Transplantation Council, International Society for Heart Lung Transplantation (ISHLT) Heart Failure and Transplantation Council, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transplant Off Publ Int Soc Heart Transplant. 2016;35(1):1–23. doi:10.1016/j.healun.2015.10.023. **Updated listing criteria for heart transplantation, pertinent details on cardiac amyloidosis.**
89. Yamashita T, Ando Y, Okamoto S, Misumi Y, Hirahara T, Ueda M, et al. Long-term survival after liver transplantation in patients with familial amyloid polyneuropathy. Neurology. 2012;78(9):637–43. doi:10.1212/WNL.0b013e318248df18.
90. Raichlin E, Daly RC, Rosen CB, McGregor CG, Charlton MR, Frantz RP, et al. Combined heart and liver transplantation: a single-center experience. Transplantation. 2009;88(2):219–25. doi:10.1097/TP.0b013e3181ac60db.