Transthyretin Cardiac Amyloidosis in Black Americans

Keyur B. Shah, MD; Anit K. Mankad, MD; Adam Castano, MD; Olakunle O. Akinboboye, MD; Phillip B. Duncan, MD; Icilma V. Fergus, MD; Mathew S. Maurer, MD

Abstract—Transthyretin-related cardiac amyloidosis is a progressive infiltrative cardiomyopathy that mimics hypertensive and hypertrophic heart disease and often goes undiagnosed. In the United States, the hereditary form disproportionately affects black Americans, who when compared with whites with wild-type transthyretin amyloidosis, a phenotypically similar condition, present with more advanced disease despite having a noninvasive method for early identification (genetic testing). Although reasons for this are unclear, this begs to consider the inadequate access to care, societal factors, or a biological basis. In an effort to improve awareness and explore unique characteristics, we review the pathophysiology, epidemiology, and therapeutic strategies for transthyretin amyloidosis and highlight diagnostic pitfalls and clinical pearls for identifying patients with amyloid heart disease.

Key Words: African Continental Ancestry Group ■ amyloidosis ■ cardiomyopathy, restrictive ■ continental population groups ■ heart failure ■ prealbumin

Black Americans are at higher risk of developing congestive heart failure, and their clinical outcomes with heart failure are less favorable than whites. Although poor cardiovascular outcomes in blacks have been associated with societal factors, such as decreased healthcare literacy, poor access to care, decreased trust in healthcare providers, or health systems, there are biological differences noted.1–3 The onset of heart failure is earlier in black patients compared with whites and strongly associated with higher blood pressure and greater left ventricular hypertrophy.4,5 Blacks typically have a higher prevalence of obesity and diabetes mellitus.6 In clinical studies, black patients exhibit biologically distinct responses to heart failure therapies from whites with differential responses to oral vasodilators and diuretics for the treatment and prevention of heart failure.6,7

On this backdrop, the black patient with heart failure has been ascribed a phenotype depicting a hypertensive, salt-sensitive, diabetic with left ventricular hypertrophy. Transthyretin-related cardiac amyloidosis is a progressive infiltrative cardiomyopathy that mimics hypertensive and hypertrophic heart disease and may go undiagnosed when a clinician attributes ventricular hypertrophy or heart failure to other prevalent pathologies (ie, hypertension, diabetes mellitus, and obesity). Studies evaluating senile or wild-type transthyretin (ATTRwt) almost exclusively consisted of white patients; however, population-based data from the United Kingdom reported an equal prevalence of ATTRwt among races.8 Under-recognition of disease may explain why blacks are poorly represented in American studies of senile cardiac amyloidosis.9

Furthermore, in the United States, the hereditary form of transthyretin amyloidosis (mutated transthyretin) is predominantly a disease of older blacks. Intrinsic features of hereditary amyloidosis could contribute a biological explanation for the disparate heart failure outcomes for blacks, with several reports associating a race-specific transthyretin variant with congestive heart failure and high frequency of this mutation observed in blacks (=1:29).10–12

Although we continue to manage the burden of comorbidities, such as hypertensive heart disease, discrepant heart failure outcomes for blacks may be, at least partly, explained by an inherited genetic mutation or under-recognition of transthyretin amyloidosis, a masquerader of hypertensive heart disease. The purpose of this study is to increase awareness of transthyretin cardiac amyloidosis in blacks.

Amyloid Heart Disease

The term amyloid describes the accumulation of proteinaceous material that deposits in otherwise normal organs. Amyloid is derived from the misfolding of endogenous proteins into an insoluble β-pleated sheet conformation, which is resistant to proteolysis and reabsorption. The deposits disrupt normal organ structure and function (eg, amyloidosis). More than 30 proteins have been identified as being amyloidogenic; of which, 5 can cause cardiac amyloidosis: immunoglobulin light chain (AL or primary amyloidosis), immunoglobulin...
Heavy chain (AH), transthyretin (ATTR), serum amyloid A (AA), and apolipoprotein A1 (A1ApoA1).13

The causative protein determines the organ involvement and clinical presentation of the disease. Early literature on cardiac amyloidosis focused on the light-chain variant (AL), where a plasma cell dyscrasia produces amyloidogenic κ- or λ-light chains.14 Two types of cardiac amyloidosis arise from transthyretin, a tetrameric protein synthesized primarily in the liver. Senile systemic amyloidosis arises from wild-type, genetically unaltered transthyretin and leads to cardiac amyloid deposition in patients after their sixth decade of life.15 A hereditary amyloidosis that is transmitted in an autosomal dominant pattern can arise with mutation of the transthyretin genome (ATTRmt). More recently, it has become evident that ATTRmt in the United States disproportionately afflicts blacks.

**Hereditary Transthyretin Amyloidosis**

Transthyretin is a 127-amino acid plasma protein made of 4 noncovalently associated β-sheet-enchained subunits that form 2 thyroxine-binding sites.16 Transthyretin is a homotetramer, and individual monomers unfold, misfold, and then aggregate to produce amyloid. Point mutations within the transthyretin protein may alter kinetics for dissociation and thus promote amyloid formation.17

In the United States, ATTRmt disproportionately affects blacks and arises from a variant of transthyretin with a point mutation resulting in a substitution of isoleucine for valine at position 122 (Val122Ile), which was first identified by Gorevic et al.18,19 Similar to the senile amyloidosis, the Val122Ile mutation results in clinically significant amyloid deposition that is predominantly isolated to the heart.

The association of Val122Ile mutation with amyloid heart disease in elderly blacks became apparent in a series of autopsy studies. On review of 52,000 autopsies performed in the Los Angeles area, the prevalence of nonlight chain cardiac amyloidosis in patients aged ≥60 years was noted to be higher in blacks compared with whites (1.6% versus 0.42%).20 When comparing blacks with whites, there were markedly higher proportions of blacks with transthyretin cardiac amyloid in the seventh (8:1) and eighth (13:1) decades of life.20,21 Of the patients with transthyretin cardiac amyloid on autopsy, 23% of blacks (versus 0% of whites) were heterozygous for the Val122Ile mutation. Furthermore, all black patients with the Val122Ile mutation had pathological evidence of transthyretin amyloid deposition in the heart (100% penetrance) at the time of death. Evaluation of living patients has revealed that the mutation is highly prevalent in blacks, with 3.43% carrying the Val122Ile mutation (allele prevalence of 0.0173).12

Carriers of the mutation are at increased risk of developing congestive heart failure. In an analysis of the Cardiovascular Health Study (CHS), an observational study of community-dwelling patients aged 65 years, there was an increased prevalence of heart failure in carriers compared with noncarriers (38% versus 15%; relative risk, 2.62 [95% confidence interval [CI], 1.28–5.37]; P=0.04).11 In the Atherosclerosis Risk in Communities Study (ARIC), a prospective cohort study that followed patients for a median of 21.5 years to an average age of 74 years, carriers were more likely to develop evidence of systolic or diastolic heart failure (hazard ratio, 1.47 [95% CI, 1.03–2.10]) and time free from HF was 2.0 years shorter among carriers of the Val122Ile mutation than among noncarriers.10

Overall survival did not statistically differ in either ARIC or CHS, but both analyses were of limited power. However, after adjusting for age and sex in the CHS cohort, the carriers of the Val122Ile mutation were at increased risk of dying at 15 years of follow-up (relative risk, 2.59 [95% CI, 1.01–6.63]; P=0.009).11 Val122Ile carriers in the ARIC cohort did not exhibit increased mortality even after adjusting for sex and age. However, ARIC was a predominantly female cohort (62%), whereas previous data have established that men have a higher penetrance of disease.22 Furthermore, longer follow-up of the ARIC cohort may have revealed an age-dependent difference in survival as was observed in the older CHS cohort. Larger studies with greater age dispersion and sex representation may further clarify mortality risk for mutation carriers.

Findings from ARIC also suggest incomplete echocardiographic penetrance of the Val122Ile mutation. The degree of left ventricular hypertrophy (11%) or overt echocardiographic findings consistent with amyloidosis (7%) were lower than expected. This was unexpected especially considering the higher prevalence of heart failure in the carriers of the mutations. One explanation is that these imaging data were limited by a small sample of subjects with Val122Ile and incomplete enrollment in the echocardiography follow-up (data available only for ≈1/3 of patients). Furthermore, the number of men with follow-up imaging, who tend to have more aggressive disease at younger age, was low (n=11; 24%). Finally, these data underscore the limitations of classic echocardiographic measurements as a surveillance tool for transthyretin cardiac amyloidosis. Considering that previous autopsy data in Val122Ile carriers showed 100% prevalence of transthyretin amyloid at the time of death, imaging modalities such as technetium pyrophosphate scintigraphy—of technetium-3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD)—based nuclear imaging, which have been shown to detect cardiac amyloid before echocardiographic manifestations, may be more effective to detect early disease.23,24

Nonetheless, the findings suggest that clinical heart failure in Val122Ile carriers is not solely dependent on the presence of the mutation and point to other as yet undefined factors that interact to promote phenotypic expression and subsequent heart failure. Population studies suggest that carriers of the mutation on average develop symptoms of congestive heart failure in the seventh decade of life, but phenotypic expression is seen earlier in men than in women and those with homozygosity for the Val122Ile mutation.11,25 Factors related to disease penetrance in other transthyretin mutations that could play a role in Val122Ile include (1) mitochondrial polymorphisms that result in earlier penetrance when the mutation is inherited from the mother, (2) relation to disease endemic foci, (3) modifier gene mutations that stabilize the transthyretin tetramer and delay disease onset, (4) environmental factors, such as inflammation and the gut microbiome, and (5) fibril composition.26–31

When evaluating black patients with clinical heart failure, the prevalence of the mutation is even higher. The
Table 1. Clinical Clues or Red Flags That May Prompt Evaluation for Hereditary Amyloidosis

<table>
<thead>
<tr>
<th>Category</th>
<th>Clinical Clues</th>
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</thead>
<tbody>
<tr>
<td>Clinical history</td>
<td>Heart failure with preserved ejection fraction presenting after the 6th or 7th decade of life</td>
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<td></td>
<td>Progressive symptoms despite clinical intervention</td>
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<td></td>
<td>Bilateral carpal tunnel syndrome</td>
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<td>Angina in the setting of a normal coronary angiography</td>
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<td></td>
<td>Intolerance of heart failure medications</td>
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<td></td>
<td>Fatigue or edema found to be out of proportion to severity of cardiomyopathy</td>
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<td></td>
<td>Family history of heart failure</td>
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<td></td>
<td>Lumbar spinal stenosis</td>
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<tr>
<td>Clinical examination</td>
<td>Elevated jugular venous pressure with rapid x and y descents (double dip)</td>
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<td></td>
<td>Kussmaul sign</td>
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<tr>
<td></td>
<td>Peripheral edema</td>
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<td></td>
<td>Normal or low blood pressure</td>
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<td></td>
<td>Ascites</td>
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<tr>
<td>Imaging</td>
<td>Discordance between voltage on electrocardiography and wall thickness (low voltage to wall mass ratio)</td>
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<tr>
<td></td>
<td>Q waves on electrocardiography without history of myocardial infarction (eg, pseudoinfarction pattern)</td>
</tr>
<tr>
<td></td>
<td>Increased right ventricular wall thickness</td>
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<tr>
<td></td>
<td>Increased ventricular wall thickness and a pericardial effusion</td>
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<tr>
<td></td>
<td>Bilateral dilatation</td>
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<td></td>
<td>Restrictive filling pattern</td>
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<td>Atrioventricular valve thickening</td>
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<td></td>
<td>Atrial septal thickening</td>
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<td></td>
<td>Apical sparing on strain rate imaging</td>
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<tr>
<td>Laboratory data</td>
<td>MRI with delayed enhancement</td>
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<tr>
<td></td>
<td>Chronically elevated serum troponin concentration, even in the absence of a chest pain syndrome</td>
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<tr>
<td></td>
<td>Chronically elevated B-type natriuretic peptide concentrations</td>
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</tbody>
</table>

MRI indicates magnetic resonance imaging.

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 blacks enrolled in the trial, the Val122Ile mutation was detected in 6.3% of patients and in 10% in those aged >60 years, suggesting that Val122Ile may be under-recognized by heart failure experts in the presence of systolic dysfunction.  

### Early Diagnostic Clues

Most studies detailing clinical characteristics of cardiac amyloidosis are limited to tertiary amyloid centers in which the number of subjects with Val122Ile is small and provide limited data on transthyretin amyloid in blacks. Such data have assessed a skewed profile of patients presenting with classic clinical features of late-stage disease. Table 1 highlights the both subtle and more advanced clinical clues that should raise concern for the presence of hereditary cardiac amyloidosis.

### Clinical Presentation

Compared with blacks presenting with AL amyloidosis, ATTRmt patients with the Val122Ile mutation are older and have less severe symptoms despite having greater ventricular wall thickness, lower left ventricular ejection fractions, and greater atrial dilation on echocardiography.  

Early disease with ATTRmt may be minimally symptomatic, especially compared with 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, whereas more extensive deposition can mimic hypertrophic cardiomyopathy. Atrial arrhythmias are frequent, and the risk of left atrial appendage thrombosis is increased.

As the disease progresses, symptoms of right heart failure predominate. Patients complain of fatigue, lightheadedness, and breathlessness. On physical examination, patients often present with hypotension, edema, ascites, hepatomegaly, and elevated jugular venous pressure.

The survival in ATTRmt is considerably better than AL cardiac amyloidosis (median, 27 versus 5 months). In contrast, data on outcomes of blacks with transthyretin cardiac amyloidosis compared with whites with wild-type transthyretin amyloidosis, a phenotypically similar condition, reveal that blacks present with more advanced disease despite having a noninvasive method for early identification (genetic testing) and outcomes in blacks may be worse. Compared with ATTRwt, Val122Ile patients in a small multicenter prospective study, Transthyretin Cardiac Amyloid Study (TRACS), had higher rates of cardiovascular hospitalization (64% versus 28%) and decreased survival (73% versus 22% died; median survival, 26 versus 43 months). Other studies have shown similar trends, raising the concern whether this is the result of inadequate access to care or has a biological basis.

### Electrocardiography

As amyloid deposits progressively replace conducting myocardium, the patient may develop Q waves on the surface ECG in the absence of epicardial coronary disease. The prevalence of this pseudoinfarction pattern or poor R-wave progression is increased as amyloid deposition becomes more diffuse.

Amyloid infiltration dampens the QRS complexes on surface electrocardiography, and reduced voltage on the ECG relative to the left ventricular mass should heighten consideration of cardiac amyloidosis. Unique to amyloidosis (low voltage on ECG and increased wall thickness on imaging), this feature can be the clue that differentiates it from hypertensive cardiomyopathy, hypertrophic cardiomyopathy, or even other infiltrative cardiomyopathies, such as Anderson–Fabry disease (high ECG voltage and increased wall thickness on imaging; Figure 1). However, the sensitivity of low voltage on the ECG for identifying cardiac amyloid is poor, especially in patients with ATTRmt. Compared with AL amyloidosis, patients with ATTRmt have higher voltage on ECG,
and ≤15% of patients meet ECG criteria for left ventricular hypertrophy. Measuring the ratio of ECG voltage to the left ventricular cross-sectional area improves the sensitivity and specificity to >80%.44-46

**Key Clinical Points**

Electrocardiographic features of cardiac amyloid, especially for the ATTRmt that affects blacks, are not sensitive for identifying patients with disease. Thus, the absence of low-voltage, pseudoinfarction pattern, or conduction disease should not exclude the diagnosis of cardiac amyloidosis. Clinicians are encouraged to integrate the voltage on ECG with the wall thickness or mass as determined by echocardiography.

**Echocardiography**

Echocardiography plays an important role in diagnosis and staging of cardiac amyloidosis (Figure 2). Amyloid infiltration of the myocardium early in the disease process presents as diastolic dysfunction, whereas late disease can be associated with reduced systolic function.47,48 Myocardial infiltration of amyloid impairs cardiac relaxation and reduces compliance. Independent of fibril deposition, the precursor proteins themselves may have a cardiotoxic effect and directly reduce myocyte function. Light chains infused from patients with AL amyloidosis result in impaired myocardial relaxation in mouse models and in culture cells, clearly demonstrating toxicity to the myocardium independent of amyloid deposition.39,50 Whether such toxicity also occurs with transthyretin amyloid precursors has not been defined.

Previous studies defining the classic echocardiographic findings associated with cardiac amyloid focused on AL amyloidosis. Child et al1 described a series of patients with 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 al45 diagnosed the now common reference to a speckled appearance to the ventricular wall because of increased myocardial echogenicity and atrial septal thickening.

Contemporary studies have delineated differences on 2-dimensional (2D) echocardiography among the subtypes of cardiac amyloidosis. In an Italian study that did not include any blacks with Val122Ile, Rapezzi et al53 studied 233 subjects divided into AL, ATTRwt, and ATTRmt. The mean left ventricular wall thickness was significantly greater in the ATTRwt (18.8±3.8 mm) than in the AL (15.1±2.7 mm) or ATTRmt (16±3.2 mm; P<0.0001) groups despite having the best survival (2-year survivals: ATTRwt, 100%; ATTRmt, 63%; and AL 63%). Left ventricular ejection fraction was lowest in the ATTRwt group, whereas findings of atrial septal thickening and pericardial effusion were no different among the 3 groups.

In a case–control study evaluating patients who had the Val122Ile mutation without a clinical diagnosis of cardiac amyloidosis, Jacobson et al52 compared 23 carriers with 46 noncarriers. Those in the Val122Ile group had significantly greater ventricular septal thickness (1.35±0.31 versus 1.19±mm; P=0.04), right ventricular hypertrophy (26% versus 2%; P=0.004), and frequency of granular sparkling (35% versus 2%; P=0.0004) compared with 46 matched controls.

Previous studies of strain rate imaging reported echocardiographic findings in patients with AL amyloidosis. Koyama et al51 showed that when compared with subjects with noncardiac AL amyloid, those with infiltration of the left ventricle (mean wall thickness, >12 mm) have significantly reduced systolic, diastolic longitudinal strain and strain rate at the base and midventricle but not apex. Sun et al46 showed that in addition to longitudinal strain, cardiac amyloidosis is associated with severely reduced strain measured in the radial and circumferential aspects, distinguishing it from hypertrophic cardiomyopathy and secondary causes of left ventricular hypertrophy. Quarta et al46 evaluated strain imaging in ATTRmt and confirmed that preservation of apical longitudinal strain was consistent across all subtypes.

**Key Clinical Points**

Although the classical morphological features of amyloidosis on 2D echocardiography and Doppler studies help identify patients with amyloidosis, preserved apical strain is a unique feature distinguishing amyloid heart disease from other causes of left ventricular hypertrophy, such as hypertensive and hypertrophic cardiomyopathy. Other clues include thickened intra-atrial septum, right ventricular hypertrophy, small pericardial effusions, and thickening of atrioventricular valves.

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**Figure 1.** Surface 12-lead electrocardiograms from a patient with mutation of the transthyretin genome (Val122Ile). The patient had severe left ventricular hypertrophy on 2-dimensional echocardiography and no coronary artery disease on coronary angiography. The ECG displayed lower than expected QRS voltage and suggestion of an anterior wall myocardial infarction (poor R-wave progression).
Cardiac troponin as a marker of myocardial cell death and B-type natriuretic peptide as a sensitive marker of myocardial dysfunction have been shown to have prognostic significance in AL amyloid. There are limited data on biomarkers in ATTRmt variant amyloidosis. Suhr et al assessed 29 subjects with Val30Met variant ATTR and found that B-type natriuretic peptide was elevated above normal in 76% and correlated with ventricular septal wall thickness, left atrial diameter, and basal septal strain. As a predictor of echocardiographic involvement of the heart, B-type natriuretic peptide 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%). Troponin concentrations are not as frequently elevated in ATTR as in AL cardiac amyloidosis; however, emerging data suggest a prognostic role for ATTR.

Key Clinical Points
Biomarker concentrations, especially B-type natriuretic peptide, are frequently abnormal in patients with ATTRmt. The role for cardiovascular biomarkers for diagnosis, prognosis, and measuring progression/regression of disease needs further study.

Advanced Diagnostic Tools
Figure 3 summarizes the evolving advanced imaging technologies for diagnosing and monitoring progression of transthyretin cardiac amyloidosis.

Cardiac Magnetic Resonance Imaging
Cardiac magnetic resonance imaging has become a valuable tool in assessing for cardiac amyloid infiltration. Cardiac morphological features can be evaluated using steady-state free precession sequence (Figure 4). This particular sequence allows assessment of both cardiac structure and function. Images of the heart are taken throughout the cardiac cycle, affording the ability to determine cardiac volumes and ejection fraction. Similarly, myocardial thickness in the atria and ventricles can be quantified. Steady-state free precession sequence is also useful in the identification of pericardial and pleural effusions, which may be present. Although diastolic function indices can be obtained by assessment of mitral inflow parameters using cine phase-contrast pulse sequence, the assessment is limited when compared with echocardiography. Apical sparing in longitudinal strain, a unique finding in cardiac amyloidosis on echocardiography, has been reproduced in cardiac magnetic resonance imaging.

Tissue characterization, specifically with late-gadolinium enhancement imaging, has been reported to be the most accurate predictor of endomyocardial biopsy-positive amyloidosis. Enhancement patterns on late-gadolinium images may be described as either diffuse, circumferential subendocardial, or patchy focal (Figure 4).

A study of 97 patients with cardiac amyloidosis showed that left ventricular mass was significantly larger in ATTR than in AL. Late-gadolinium enhancement was substantially more extensive in ATTR, with ≤90% of ATTR patients demonstrating transmural enhancement. Subendocardial enhancement was more common in AL patients. Right ventricular gadolinium enhancement was apparent in 100% of ATTR patients compared with 72% of AL.

Early darkening of the blood pool after contrast caused by rapid washout of gadolinium into an enlarged subendocardial
Figure 3. Summary of the advanced imaging modalities for diagnosis and monitoring of cardiac amyloidosis. $^{99m}$Tc-DPD indicates technetium 3,3-diphosphono-1,2-propanodicarboxylic acid; $^{99m}$Tc-PYP, technetium pyrophosphate scintigraphy; ATTR, transthyretin genome; H/CL, heart to contralateral ratio; LV, left ventricle; MRI, magnetic resonance imaging; PET, positron emission tomography; RV, right ventricle; and TTR, transthyretin genome.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Representative Image</th>
<th>Diagnosis</th>
<th>Subtyping (ATTR vs. AL)</th>
<th>Prognosis</th>
<th>Long-term Follow-up / Response to Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echo strain</td>
<td></td>
<td>Helpful with associated clinical features and classic reduced global strain with apical sparing</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>$^{99m}$Tc-PYP</td>
<td></td>
<td>Helpful in diagnosing ATTR cardiac involvement with intense myocardial uptake measured by H/CL ratio $&gt;1.5$</td>
<td>Distinguishes ATTR from AL amyloid with good sensitivity and specificity</td>
<td>Correlates with LV mass</td>
<td>Unknown</td>
</tr>
<tr>
<td>$^{99m}$Tc-DPD</td>
<td></td>
<td>Helpful in diagnosing cardiac involvement</td>
<td>Distinguishes ATTR from AL amyloid with good sensitivity and specificity</td>
<td>Correlates with LV mass and survival</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cardiac MRI</td>
<td></td>
<td>Subendocardial or transmural late gadolinium enhancement in a non-coronary artery distribution and failure to null the myocardium can be virtually pathognomonic for amyloidosis</td>
<td>No</td>
<td>Unknown</td>
<td>T1 mapping has potential to track extracellular volume (amount of amyloid) over time</td>
</tr>
<tr>
<td>PET</td>
<td></td>
<td>[{$^{18}$F}]florbetapir diffuse LV&gt;RV uptake in TTR and AL cardiac amyloidosis</td>
<td>No</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Modality: Echo strain, $^{99m}$Tc-PYP, $^{99m}$Tc-DPD, Cardiac MRI, PET.
interstitial space can be quantitatively assessed by mapping of T1 kinetics of the blood pool and subendocardium early after gadolinium administration. White et al recently published a study in cardiac magnetic resonance to assess prognosis in cardiac amyloidosis. They used the observation that in contrast 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 >50% of myocardial tissue becoming black at an earlier inversion time when compared with blood (Figure 5). The inversion time, an accurate indicator of global myocardial hyperenhancement, was a strong predictor of mortality (hazard ratio, 6.0; 95% CI, 3.0–12.1).

A new imaging approach of phase-sensitive inversion recovery may further improve the sensitivity for late-gadolinium enhancement by automating the nulling of the myocardial signal. Fontana et al studied 250 ATTR and AL cardiac amyloidosis patients and found that with phase-sensitive inversion recovery, transmural patterns of late-gadolinium enhancement were associated with the worse prognosis (hazard ratio, 5.4; 95% CI, 2.1–13.7; P<0.0001), even after adjusting for biomarkers and echocardiographic parameters (hazard ratio, 4.1; 95% CI, 1.3–13.1; P<0.05).

In subjects unable to receive gadolinium, native (precontrast) T1 mapping can identify early cardiac amyloid infiltration and can differentiate ATTR or AL amyloid from hypertrophic cardiomyopathy.

**Key Clinical Points**
Cardiac magnetic resonance imaging offers a noninvasive diagnostic and prognostic tool for cardiac amyloidosis. In addition to defining morphological characteristics, delayed gadolinium enhancement and altered gadolinium kinetics are highly specific findings for cardiac amyloid disease. In transthyretin amyloid, patterns other than subendocardial delayed enhancement predominate. Furthermore, T1 mapping may offer an opportunity to identify early disease and quantitatively follow disease progression and regression without the need for contrast.

**Nuclear Imaging**
Nuclear imaging modalities can aid in the diagnosis of transthyretin cardiac amyloidosis.
The use of $^{99m}$technetium pyrophosphate scintigraphy for detecting ATTR was demonstrated in a recent study of 45 patients (12 AL, 16 ATTRwt, and 17 ATTRmt [12 mutants with Val122Ile]) with biopsy-proven amyloidosis. Subjects with ATTR had significantly higher semiquantitative cardiac visual score than the AL cohort, as well as a higher quantitative score. A heart to contralateral ratio $\geq 1.5$ was consistent with intensely diffuse myocardial tracer retention with 97% sensitivity and 100% specificity for identifying ATTR cardiac amyloidosis.

Of note, the most studied bone-seeking radiotracer in cardiac amyloidosis to date is $^{99m}$technetium-3,3-diphosphono-1,2-propanodicarboxylic acid ($^{99m}$Tc-DPD). However, this isotope is not approved by the Food and Drug Administration and therefore not available for clinical use in the United States and has not been used widely to evaluate the Val122Ile mutation. Among 79 patients (28 ATTRmt [0 mutants with Val122Ile], 17 ATTRwt, and 34 AL) who underwent $^{99m}$Tc-DPD with tracer retention calculated by a heart-to-whole body ratio (H/WB), the test was 100% sensitive and 88% specific for detecting ATTR because $\approx 1/3$ of AL patients having unexpected tracer uptake.67 In a follow-up study in 63 patients with ATTR (23 of whom had no echocardiographic features of amyloid involvement), the use of $^{99m}$Tc-DPD scintigraphy for identifying myocardial infiltration across a wide spectrum of morphological and functional phenotypes was evaluated.68 All patients showed moderate to severe myocardial tracer uptake (semiquantitative score $\geq 2$); H/WB ratio was positively correlated with left ventricular mean wall thickness ($r=0.695$; $P<0.001$), negatively correlated with left ventricular ejection fraction ($r=-0.368$; $P=0.004$), and was an unfavorable predictor of major adverse cardiac event–free survival at Cox univariate analysis. Smaller studies have also suggested that using bone scintigraphy with $^{99m}$technetium-hydroxymethylene diphosphonate may allow for early detection of ATTR cardiac disease.23,24

**Key Clinical Points**

Various nuclear imaging radiotracers are useful to diagnose transthyretin cardiac amyloidosis. $^{99m}$Tc-TECHNETIUM PYROPHOSPHATE SCINTIGRAPHY and $^{99m}$Tc-DPD can distinguish AL from ATTR with excellent sensitivity and specificity in advanced disease. Early data suggest that these modalities detect amyloid deposition before echocardiography, thus offering an opportunity for improved preclinical diagnosis. Further studies are needed in a broader spectrum of disease, including early phase cardiac amyloid, and in Val122Ile in particular.

### Establishing the Diagnosis

#### Histopathology

Tissue confirmation of amyloid deposition is traditionally considered for confirmation of the diagnosis of amyloidosis. Cardiac deposition of amyloid is diffuse and homogenous in its distribution, allowing for a high sensitivity when obtaining a pathological diagnosis. Because amyloidosis is a systemic disease, multiple sources can provide a diagnosis, but the yield can vary greatly from organ to organ. Fine et al69 published the largest study in ATTR and fat pad aspiration to date (including 286 subjects) comparing the yield of cardiac and noncardiac biopsies in patients with ATTRwt and ATTRmt. The yield for ATTRmt 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 ATTRmt and 89 ATTRwt specimens). The highest yield for ATTRmt for noncardiac biopsies came from rectal (81% of 52 specimens) and sural nerve (83% of 54 specimens) biopsies.

Congo red stain, which exhibits apple-green birefringence under polarized light, is commonly used; however, implementing fluorescent microscopy improves sensitivity for amyloid deposits.70 More specific techniques for identifying the subtype of amyloid include immunohistochemical staining for light chains or transthyretin. Although valid for amyloid typing, there are considerable pitfalls to immunohistochemical,
including failure to react to truncated AL light chains, and many hereditary amyloidoses can be missed by a limited antibody panel. It is noteworthy that when assessing for the gene found in ATTRmt of blacks, all 10 samples from subjects with Val22Ile ATTRmt studied by Connors et al positively stained for antihuman transthyretin antibodies (9 cardiac and 1 fat pad).

Finally, mass spectrometry can be performed to examine the affected tissue and study the protein constituents of the amyloid fibril. 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%.

Key Clinical Points
For ATTRmt, noncardiac biopsies may identify disease; however, the sensitivity is lower than that for AL amyloidosis. A negative noncardiac biopsy does not exclude disease, and an endomyocardial biopsy should be considered. Biopsies revealing amyloid deposition should be further evaluated to confirm protein composition with immunohistochemical staining and mass spectrometry.

Genetic Testing
There are >100 polymorphisms encoding the variant gene that transcribes the transport protein transthyretin, located on the long (q) arm of chromosome 18 at position 12.1 (18q12.1), with 80 confirmed pathogenic mutations. Isoelectric focusing gel electrophoresis, a method of separating molecules by their isoelectric point (pI) and pH, can differentiate ATTRwt from >95% of variants of ATTRmt. Among those with ATTRwt, only 1 protein band is visualized, whereas heterozygous ATTRmt will show both the wild-type transthyretin at the typical pI and a second mutant transthyretin (2 distinct protein bands). A single-protein band at this pI would suggest homozygosity for the Ile122 mutation. Conclusive genetic distinction between ATTRmt and ATTRwt is obtained from polymerase chain reaction amplification and DNA sequencing of the transthyretin exons 1 to 4, validating isoelectric focusing.

Key Clinical Points
Genetic testing can provide a method for early identification of at-risk or affected individuals and is critical in distinguishing hereditary from senile transthyretin amyloidosis. Because of the high prevalence of the Val122Ile in blacks, one must not attribute the type of cardiac amyloidosis to the mutation until AL amyloid has been comprehensively excluded.

Diagnostic Algorithm
Considering the heterogeneous presentation and insidious progression of this disease, diagnosis is often delayed until the late stages. We propose a diagnostic algorithm in Figure 6 incorporating clinical clues (Table 1) and advanced imaging modalities (Figure 2) for identifying blacks with hereditary amyloidosis. Furthermore, common misconceptions and pitfalls for diagnosis are presented in Table 2.

Therapeutic Options
Clinical Pearls for Medical Management
The clinical management of a patient with symptomatic restrictive amyloid from ATTRmt is similar to AL cardiomyopathy and is centralized around managing fluid balance. Excessive intravascular volume leads to breathlessness and edema,
Table 2. Common Misconceptions About Transthyretin Amyloid That Lead to Delayed or Missed Diagnosis of Cardiac Amyloidosis

<table>
<thead>
<tr>
<th>Pitfall</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>The voltage on the ECG was normal</td>
<td>Low voltage is a relatively late-phase phenomenon in transthyretin-related cardiac amyloidosis, and many patients with biopsy-proven disease do not meet electrocardiographic criteria for low voltage. In fact, some patients have electrocardiographic evidence of left ventricular hypertrophy.</td>
</tr>
<tr>
<td>The fat pad aspiration biopsy did not show evidence of amyloidosis</td>
<td>The sensitivity of a fat pad biopsy for TTR amyloid is low and thus cannot be used to exclude the diagnosis.</td>
</tr>
<tr>
<td>The protein electrophoresis showed no evidence of a plasma cell dyscrasia; thus, the patient does not have cardiac amyloidosis</td>
<td>Transthyretin amyloidosis is not caused by a plasma cell dyscrasia, and evaluation for a monoclonal gammopathy is expected to be normal. However, the first step once a diagnosis of cardiac amyloidosis is considered is to exclude light-chain amyloid, given its malignant nature and available therapy.</td>
</tr>
<tr>
<td>The history of hypertension/diabetes mellitus/kidney disease explained the patients ventricular hypertrophy</td>
<td>Transthyretin cardiac amyloidosis often coexists with these medical conditions that are common in elderly blacks.</td>
</tr>
<tr>
<td>The ejection fraction was low; thus, it is unlikely to be a restrictive cardiomyopathy like cardiac amyloidosis</td>
<td>As cardiac amyloidosis progresses, the systolic function becomes compromised.</td>
</tr>
<tr>
<td>Cardiac amyloidosis is a contraindication for heart transplantation</td>
<td>Outcomes after solid organ transplantation are good with transthyretin amyloidosis. Patients with significant cardiac involvement may be eligible for heart or heart-liver transplantation.</td>
</tr>
</tbody>
</table>

MRI indicates magnetic resonance imaging; and TTR, transthyretin.

whereas modest hypovolemia can cause hypotension and exacerbate renal injury. The mainstays of therapy are loop diuretics, but combination blockade of the renal nephron with thiazide diuretics and aldosterone antagonist may become necessary in the setting of refractory edema or hypokalemia, respectively.

Traditional disease-modifying medications for heart failure have no proven role in the treatment of amyloid heart disease, which is progressive in nature. In fact, most medications have potential to cause harm. Drugs that slow the heart rate (β-blockers and 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. In addition to worsening symptoms, there are published case reports of sudden death of patients with amyloidosis after administration of such therapies.75,76 Digitalis may bind to amyloid fibrils, leading to unpredictable and possibly toxic circulating concentrations, prohibiting its use in amyloid heart disease. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and combination vasodilators may be poorly tolerated because of hypotension and lightheadedness. 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.

Atrial arrhythmias are frequent, and symptomatic arrhythmias may need to be addressed with pharmacological or ablative therapies. Most importantly, patients with atrial fibrillation or atrial standstill should receive anticoagulation as the risk for intracardiac thrombus and thromboembolism is markedly increased.35,36 The benefit of an implantable defibrillator or cardiac resynchronization is undefined. The efficacy of defibrillation can be limited in an amyloid heart in which extensive protein deposition may limit detection of arrhythmias and increase the defibrillation thresholds for delivery of successful therapy.

Novel Therapies for ATTR: Stabilizers, Silencers, and Degraders

No Food and Drug Administration–approved drugs are currently available for treatment of the ATTR cardiac amyloidosis, but several treatment strategies are under clinical investigation.

Agents with transthyretin-stabilizing properties are in various stages of clinical development. Diflunisal, a nonsteroidal anti-inflammatory drug, binds and stabilizes transthyretin variants against acid-mediated fibril formation in vitro and has been tested in animal safety studies and human clinical trials.77 However, the chronic inhibition of cyclooxygenase enzymes, including gastrointestinal bleeding, renal dysfunction, fluid retention, and hypertension, may exacerbate heart failure. Currently, under clinical trials, tafamidis (Pfizer Inc, New York, NY) binds to the thyroxine-binding sites on the transthyretin tetramer and inhibits its dissociation into monomers, thereby blocking the rate-limiting step in the amyloid fibril cascade.78 A phase 3 trial evaluating the efficacy, safety, and tolerability of tafamidis oral dose of 20 or 80 mg compared with placebo is fully enrolled and expected to conclude in mid-2018.

RNA interference has emerged as an endogenous cellular mechanism for controlling gene expression in which small interfering ribonucleic acids mediate the cleavage of target messenger RNA.79 Lipid nanoparticle formulations and newer N-acetylgalactosamine conjugates have emerged as agents to deliver small interfering ribonucleic acids to hepatocytes, the source of mutated Val122Ile transthyretin production.80 A phase III trial in familial amyloid cardiomyopathy is currently enrolling.

Antisense oligonucleotides are also under clinical investigation as inhibitors of hepatic expression of amyloidogenic transthyretin, and a phase III trial enrolling both ATTRwt and ATTRmt cardiac amyloid is targeted for enrollment in 2016.

Treatment approaches to amyloidosis have focused on reducing amyloid precursor protein production, but the ability to remove already deposited amyloid is another important therapeutic strategy. The use of combined doxycycline and tauroursodeoxycholic acid has been studied for transthyretin degradation, and clinical trials are under development for ATTRmt cardiac amyloidosis.81 The role of normal, nonfibrillar glycoprotein present in all human amyloid deposits, serum
amyloid P component, is currently under intense investigation to address the unmet need for therapy that safely promotes clearance of established amyloid deposits.82

Conclusions/Future Directions

In summary, the Val122Ile mutation in the transthyretin gene is common in blacks (prevalent in 1 in 25) and results in an age-dependent, late-onset restrictive/hypertrophic cardiomyopathy that can mimic other forms of heart failure leading to misdiagnosis and underdiagnosis. Penetration of the phenotype is low according to recent data, and the biological, genetic, and environmental factors that lead to phenotypic penetrance remain unknown but if defined could provide insights into other forms of cardiovascular disease that disproportionately afflict blacks. This form of cardiac amyloidosis could be more easily identified than ATTRwt (senile cardiac amyloidosis) if widespread genetic testing were implemented. The available data suggest that despite the ability for early diagnosis, those with the Val122Ile mutation present initially with a more advanced phenotype than ATTRwt. Whether this is because of a more malignant phenotype in the presence of the Val122Ile or is the result of racial differences in access to care is unknown. With the advent of noninvasive nuclear medicine techniques for identifying transthyretin cardiac amyloid caused by either mutant or wild-type disease, there is an opportunity to identify blacks with both Val122Ile and wild-type transthyretin and follow up their progression and outcomes to address these issues. Ongoing investigation of disease-modifying therapies, including transthyretin stabilizers and transthyretin silencers, will determine whether these agents can alter the natural history of Val122Ile cardiac amyloidosis, which is a relentlessly progressive form of heart failure.

Sources of Funding

Dr Castano was supported by a dual grant awarded by the American College of Cardiology and Merck & Co, Inc. Dr. Maurer was supported by a K24 from National Institute on Aging AG036778 entitled Midcareer Mentoring Award for Patient Oriented Research in Geriatric Cardiology.

Disclosures

Drs Shah, Akinboboye, and Maurer have received research grants for clinical trials from Alnylam Pharmaceuticals and Pfizer, Inc. Dr Shah is on the speaker’s bureau for Amgen Pharmaceuticals. Dr Shah has received research grants from Thoratec Corp. Dr Mankad has received research grants for clinical trials from Alnylam Pharmaceuticals. Dr Castano has received a research grant from the American College of Cardiology and Merck & Co, Inc. Dr Duncan is on the speaker’s bureau for Arbor Pharmaceuticals and serves on the medical advisory boards for Alnylam Pharmaceuticals, Novartis Pharmaceuticals, and Amgen Pharmaceuticals. Dr Fergus is on the speaker's bureau for Novartis Pharmaceuticals.

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Transthyretin Cardiac Amyloidosis in Black Americans
Keyur B. Shah, Anit K. Mankad, Adam Castano, Olakunle O. Akinboboye, Phillip B. Duncan, Icilma V. Fergus and Mathew S. Maurer

Circ Heart Fail. 2016;9:e002558
doi: 10.1161/CIRCHEARTFAILURE.115.002558

Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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