

## ADVANCES IN HEART FAILURE

# Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis

**ABSTRACT:** Cardiomyopathy is a manifestation of transthyretin amyloidosis (ATTR), which is an underrecognized systemic disease whereby the transthyretin protein misfolds to form fibrils that deposit in various tissues and organs. ATTR amyloidosis is debilitating and associated with poor life expectancy, especially in those with cardiac dysfunction, but a variety of treatment options have recently become available. Considered a rare disease, ATTR amyloidosis may be more prevalent than thought, particularly in older persons. Diagnosis is often delayed because of a lack of disease awareness and the heterogeneity of symptoms at presentation. Given the recent availability of effective treatments, early recognition and diagnosis are especially critical because treatment is likely more effective earlier in the disease course. The Amyloidosis Research Consortium recently convened a group of experts in ATTR amyloidosis who, through an iterative process, agreed on best practices for suspicion, diagnosis, and characterization of disease. This review describes these consensus recommendations for ATTR associated with cardiomyopathy as a resource to aid cardiologists and others in the recognition and diagnosis of ATTR associated with cardiomyopathy. Included in this review is an overview of red flag signs and symptoms and a recommended diagnostic approach, including testing for monoclonal protein, scintigraphy, or biopsy and, if ATTR associated with cardiomyopathy is identified, TTR genotyping.

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**T**ransthyretin amyloidosis (ATTR) is a disease caused by abnormal fibrils derived from TTR (transthyretin), a protein produced mainly by the liver, which aggregate and deposit in tissues and organs.<sup>1</sup> Cardiomyopathy is a common manifestation of ATTR amyloidosis (ATTR associated with cardiomyopathy [ATTR-CM]) and is associated with a particularly poor life expectancy of 2 to 6 years after diagnosis.<sup>2</sup> Patients with ATTR-CM experience debilitating physical symptoms common to heart failure (HF), such as exercise intolerance and fatigue, which result in decreased functional capacity, diminished quality of life, and eventual death.<sup>3</sup> ATTR-CM can be acquired through aggregation of wild-type TTR (ATTRwt) or inherited from a variety of genetic variants of TTR (mutant transthyretin amyloidosis [ATTRm]; also known as hereditary ATTR).

ATTRm is considered rare and is transmitted in an autosomal-dominant manner and with variable penetrance. Certain variants typically result in cardiomyopathy, whereas others typically result in polyneuropathy, although cardiomyopathy and polyneuropathy manifestations may overlap (Figure 1). The prevalence of cardiomyopathy among persons with ATTRm is estimated at ≈40 000 of the 50 000 persons with ATTRm globally,<sup>4</sup> but this may be an underestimate.

The most common worldwide *TTR* variant, Val122Ile (or pV142I), occurs in ≈3% to 4% of black Americans, with undefined phenotypic penetrance.<sup>5,6</sup> This Val122Ile *TTR* variant manifests predominantly as cardiomyopathy,<sup>7</sup> and 1 estimate shows 10% of black Americans with HF who are older than 60 are carriers of the Val122Ile *TTR* variant.<sup>8</sup> Thr60Ala, another common *TTR* variant, often manifests as a mixed phenotype, including cardiomyopathy, polyneuropathy, and gastrointestinal dysfunction and is present in ≈1% of persons in northwest Ireland.<sup>9</sup> The Val30Met variant is the most common cause of ATTRm with polyneuropathy; however, late-onset ATTRm in patients of the Val30Met variant typically manifests as cardiomyopathy. Phenotypic penetrance of ATTRm is clearly age dependent;

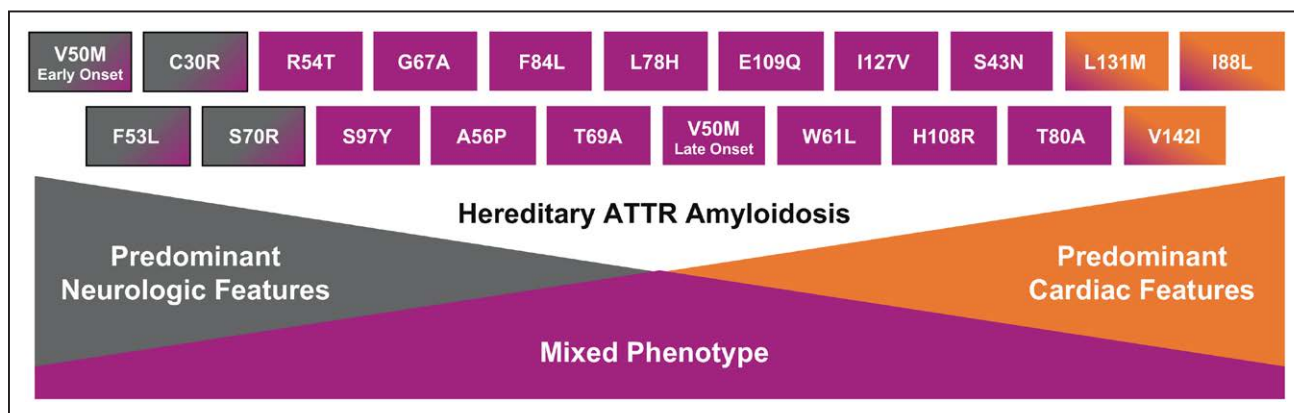
thus, ascertainment of population prevalence varies depending on age.

The true prevalence of ATTRwt is unknown; it may be relatively high compared with the prevalence of ATTRm. In autopsy studies, ≈25% of the hearts of persons 80 years or older contained wild-type TTR fibrils, regardless of the presence of symptoms.<sup>4,10</sup> Studies using nonbiopsy approaches to diagnosis demonstrate a TTR prevalence of 16% among patients undergoing percutaneous aortic valve replacement for severe aortic stenosis,<sup>11</sup> 13% among patients with heart failure with a preserved ejection fraction,<sup>12</sup> 5% among patients with presumed hypertrophic cardiomyopathy,<sup>13</sup> and 7% to 8% among patients with carpal tunnel syndrome on biopsy of the tenosynovial tissue.<sup>14</sup> Furthermore, ≈1% to 3% of persons older than 75 showed myocardial retention of the diphosphono-1,2-propanodicarboxylic acid, which is indicative of TTR cardiac amyloidosis.<sup>15,16</sup>

Delays in diagnosis of ATTR-CM amyloidosis commonly occur because of physician- and disease-related reasons, including fragmented knowledge among different specialists and subspecialists, shortage of centers and specialists dedicated to disease management, erroneous belief that it is an incurable disease, perceived rarity of the condition, intrinsic phenotypic and genotypic heterogeneity, and, in some cases, the necessity of target organ tissue histological diagnosis.<sup>12,17,18</sup>

The Amyloidosis Research Consortium recently led the development of a comprehensive set of consensus recommendations for the suspicion and diagnosis of ATTR amyloidosis. These recommendations were developed in collaboration with companies conducting research in ATTR amyloidosis (GSK, Ionis, Pfizer, and Alnylam) and through an iterative process with key specialists in amyloidosis. They also reflect collaboration and consensus among key amyloidosis experts of best practices for diagnosis and characterization of the disease.

This review describes the consensus recommendations for ATTR-CM amyloidosis with a goal of providing clinicians with an overview of key aspects of ATTR-CM



**Figure 1. Genotype–phenotype correlations in mutant transthyretin amyloidosis.** ATTR, transthyretin amyloidosis. Reprinted with permission from Akcea Therapeutics.

diagnosis to help facilitate rapid and accurate identification of the disease. Focus is placed on disease presentation, characterization, and challenges for early and accurate diagnosis.

## MISDIAGNOSIS AND RAISING SUSPICION

### Misdiagnosis

Because they are considered rare and typically manifest with heterogeneous symptoms similar to those of other more common diseases, ATTRm and ATTRwt amyloidosis can be difficult to diagnose. Unexplained sensorimotor neuropathy or autonomic symptoms, such as orthostasis, erectile dysfunction, sweating abnormalities, and diarrhea, may lead to many lengthy and unfocused medical evaluations before amyloid is discovered. Depending on the mutation, patients with ATTR-CM show common signs and symptoms of HF, such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, fatigue, exercise intolerance, dizziness/syncope, palpitations, electrical conduction abnormalities, and arrhythmias. Therefore, ATTR-CM is sometimes mistakenly diagnosed as hypertrophic cardiomyopathy<sup>13</sup> or as generic, undifferentiated heart failure with preserved ejection fraction rather than as amyloidosis.<sup>12</sup>

It is significant that in addition to symptoms of cardiomyopathy, other systemic phenotypes such as polyneuropathy and gastrointestinal disorders may be present. Because of the age-dependent development of ATTR-CM, many patients have true comorbid conditions including hypertension, diabetes mellitus, ischemic heart disease, or aortic stenosis (particularly low flow-low gradient) before amyloidosis develops. In this context, a high degree of clinical suspicion is necessary to identify incident ATTR-CM.

### Signs and Symptoms

The spectrum of clinical presentations in patients with ATTR amyloidosis obliges all clinicians to be aware of common disease patterns (Table 1; Figure 2), additional clues, and commonly affected populations. Suspicion of ATTR-CM should be triggered in older persons who have been hospitalized for HF, elevated troponin levels, or levels of NT-proBNP (N-terminal pro-brain natriuretic peptide) that are out of proportion to the clinical context. Other hints of ATTR amyloidosis include hypertension that resolves over time and an intolerance of ACE (angiotensin-converting enzyme) inhibitors, angiotensin receptor blockers, or  $\beta$  blockers. In addition, though not infrequent in the general population, carpal tunnel syndrome occurs particularly frequently among males with ATTR.<sup>19</sup> Lumbar spinal stenosis,<sup>20,21</sup> previous orthopedic procedures,<sup>22</sup> and

**Table 1. Diagnostic Clues to ATTR-CM**

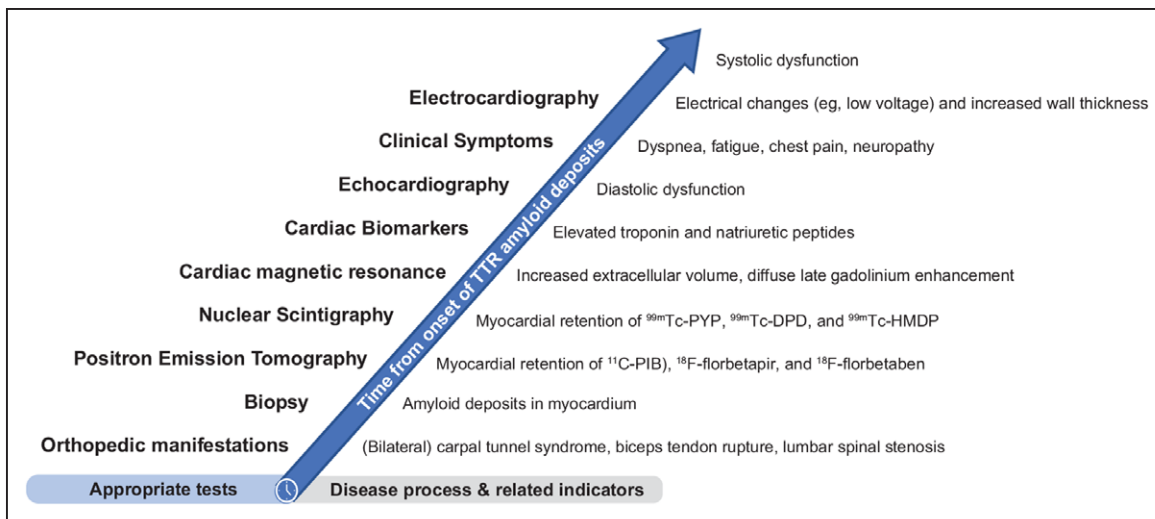
History/examination clues
Evidence of right-sided heart failure (eg, hepatomegaly, ascites, and lower extremity edema)
HFpEF, particularly in men
Intolerance to ACE inhibitors or beta blockers
Bilateral carpal tunnel syndrome
Lumbar spinal stenosis
Biceps tendon rupture
Unexplained peripheral neuropathy (eg, loss of warm/cold discrimination), particularly if associated with autonomic dysfunction (eg, postural hypotension, alternating bowel pattern)
Unexplained atrial arrhythmias or conduction system disease/need for a pacemaker
Imaging clues
Myocardial uptake on PYP/DPD or HMDP imaging
Infiltrative phenotype (eg, biventricular hypertrophy pericardial effusion, valve thickening, interatrial septal thickening)
Diffuse subendocardial or transmural LGE or increased ECV fraction on cardiac MRI
Apical sparing on longitudinal strain imaging
Low myocardial contraction fraction
Restrictive LV filling with RV wall thickening
Combined clues
HF with unexplained increased LV wall thickening and nondilated LV
Concentric LV wall thickening, possibly with an abnormal QRS voltage-to-LV thickness ratio
Depressed longitudinal LV function despite normal EF
Aortic stenosis with RV thickening, particularly if paradoxical low flow/low gradient

The sensitivity and specificity of these clues has not been delineated in population-based samples with heart failure. ACE indicates angiotensin-converting enzyme; ATTR-CM, transthyretin amyloidosis with predominant cardiomyopathy; DPD, diphosphono-1,2-propanodicarboxylic acid; ECV, extracellular volume; EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HMDP, hydroxymethylene diphosphonate; LGE, late gadolinium enhancement; LV, left ventricular; MRI, magnetic resonance imaging; PYP, pyrophosphate; and RV, right ventricular.

spontaneous biceps tendon rupture<sup>23</sup> may also be early indicators of ATTR-CM.

### Biomarkers

No plasma or urinary biomarker is available for the diagnosis of ATTR. Nevertheless, in the clinical arena, the combination of very high plasma levels of NT-proBNP (disproportionate compared with the degree of HF) and elevated troponin levels in a patient with echocardiographic hypertrophic phenotype is strongly suggestive of amyloidotic cardiomyopathy and can prompt the diagnostic workup. NT-proBNP is a biomarker that is elevated early in ATTRm amyloidosis before cardiac symptoms appear, especially among asymptomatic carriers of a *TTR* gene mutation or patients with neurological symptoms only.<sup>24</sup> In addition, the usefulness of



**Figure 2.** Proposed timeline of appropriate diagnostic tests based on typical disease process.

<sup>11</sup>C-PIB indicates Pittsburgh compound B; <sup>99m</sup>Tc-DPD, <sup>99m</sup>technetium-3,3-diphosphono-1,2-propanodicarboxylic acid; <sup>99m</sup>Tc-HMDP, hydroxymethylene diphosphonate; <sup>99m</sup>Tc-PYP, technetium pyrophosphate; ATTR-CM, transthyretin amyloidosis with predominant cardiomyopathy (either wild-type or hereditary); CA, cardiac amyloidosis; ECG, electrocardiography; LVST, left ventricular septal thickness; and TTR, transthyretin.

circulating retinol binding protein 4 in conjunction with electrocardiographic and echocardiographic measures to identify patients with HF who have ATTR cardiac amyloidosis from the Val122Ile mutation has recently been reported.<sup>25</sup>

## Electrocardiography and Cardiac Imaging

Electrocardiography is a broadly available screening test, and findings may reveal abnormalities associated with ATTR-CM (eg, low voltage) that are classically described in patients with cardiac amyloidosis.<sup>26–28</sup> However, low voltage is less common in cardiac amyloidosis than a pseudoinfarct pattern of Q waves unrelated to prior myocardial infarctions.<sup>27</sup> Given that low QRS voltage has been seen in ≈50% of patients with AL amyloidosis and in ≈25% of patients with ATTR amyloidosis, its usefulness as a screening test is limited by low sensitivity.<sup>27</sup> More commonly, cardiac amyloidosis is hallmarked by QRS voltages that are disproportionate to the thickness of the left ventricular (LV) wall, which can be assessed using a ratio of QRS voltage to LV wall thickness.<sup>29,30</sup> The presence of left ventricular hypertrophy on electrocardiography does not exclude ATTR-CM.

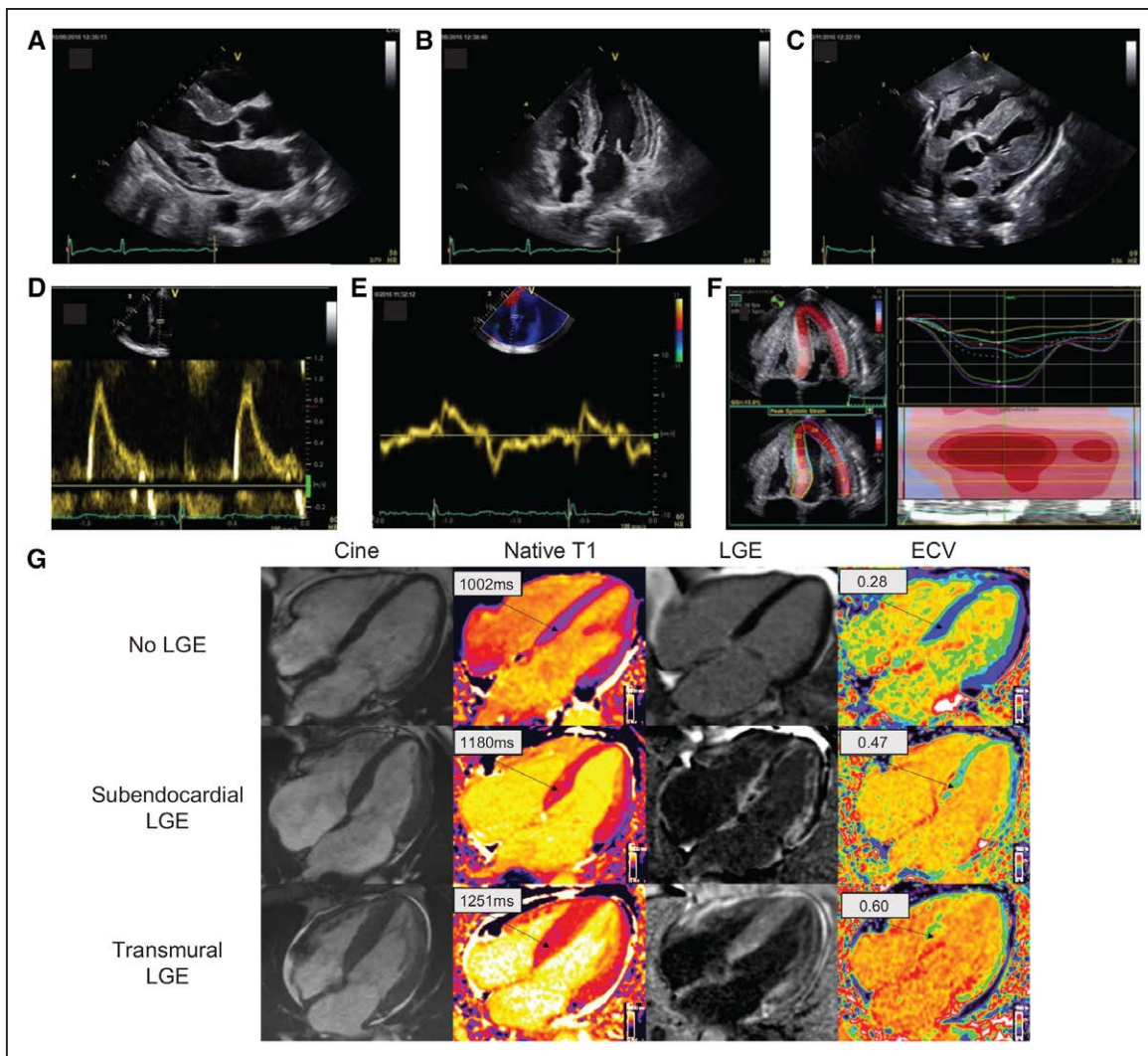
Echocardiography is cost-effective, commonly available, relatively quick to perform, and better than most other imaging techniques at identifying diastolic dysfunction. Although all are not invariably present, classic echocardiography findings of infiltrative disease include LV wall thickening, small LV cavity size, biatrial enlargement, thickened valves, elevated right ventricular systolic pressure and atrial septum thickness, granular sparkling appearance of the myocardial wall, pericardial effusion, restrictive transmi-

tral Doppler filling pattern, and reduced ventricular strain, apical-to-basal strain ratio >2.1, LV ejection fraction-to-strain ratio >4 (Figures 2 and 3).<sup>26,31,32</sup> Combining electrocardiography (low voltage) and echocardiography (LV septal thickness above the upper limit of normal, especially >12 mm) is particularly useful for increased clinical suspicion of ATTR-CM<sup>33</sup> (Table 1; Figure 2).

Similarly, cardiac magnetic resonance (CMR) can show detailed information about systolic function and cardiac structure (Figure 3). The advantage of CMR is its unique ability to enable tissue characterization,<sup>34,35</sup> allowing it to differentiate amyloidosis from nonamyloid wall-thickening disorders. On tissue characterization, the typical CMR findings of cardiac amyloidosis include diffuse subendocardial or transmural late gadolinium enhancement on late gadolinium imaging with nulling of the blood pool and elevated native T1 and extracellular volume on T1 mapping sequences. T1 mapping, a relatively new and quantitative CMR technique, with native T1 and extracellular volume, has the potential to longitudinally monitor disease progression.<sup>35,36</sup>

Myocardial scintigraphy with bone avid tracers <sup>99m</sup>technetium pyrophosphate (<sup>99m</sup>Tc-pyrophosphate), <sup>99m</sup>technetium 3,3-diphosphono-1,2-propanodicarboxylic acid (<sup>99m</sup>Tc-diphosphono-1,2-propanodicarboxylic acid), and <sup>99m</sup>technetium hydroxymethylene diphosphonate (<sup>99m</sup>Tc-hydroxymethylene diphosphonate) has high sensitivity and specificity for ATTR-CM and may help with the early diagnosis of ATTR-CM (Figures 4 and 5).<sup>37–43</sup> Ease of access, simplicity of imaging, relatively low cost, and specificity for cardiac ATTR amyloid deposits are some of the advantages of myocardial scintigraphy compared with echocardiography, CMR,





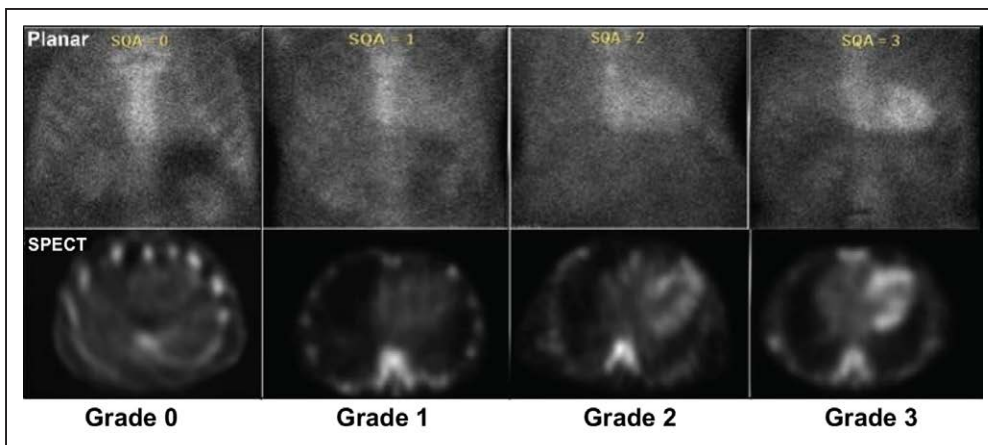
**Figure 3. Typical echocardiography and cardiac magnetic resonance (CMR) findings in a patient with cardiac amyloidosis.**

Parasternal longitudinal axis (A) and apical 4-chamber (B) echocardiography views show considerably increased left ventricular wall thickness in the absence of ventricular dilation; the myocardial walls seem hyperechogenic. Other characteristic findings include biatrial enlargement and thickening of valve leaflets (A and B) of the interatrial septum (B) and right ventricle-free wall (C). A generalized small pericardial effusion is also noticeable (A–C). The profile of left ventricle (LV) filling (D) is restrictive, with markedly elevated E wave, reduced A wave, and decreased deceleration time. A decreased E' wave measurement can be observed on lateral wall tissue Doppler imaging (E). The longitudinal systolic function is impaired with decreased S' measurement on lateral wall tissue Doppler imaging (E) and markedly reduced longitudinal strain evident on the apical 4-chamber view (F). LV longitudinal strain (F) is preserved at the LV apex but is significantly impaired at the midbasal segments. Each colored curve shows longitudinal strain at 1 of the 6 LV measured segments. Dotted line is the mean. Color map represents the 6 LV segments, with time corresponding to the x axis. The bullseye appearance (with apex at the center of the color-coding map) is typical of cardiac amyloidosis. Cardiac magnetic resonance images (G) include 4-chamber cine, corresponding native T1 maps, late gadolinium enhancement (LGE) image with phase-sensitive reconstruction, and extracellular volume (ECV) maps in a patient with no cardiac amyloidosis (upper row) and 2 patients with cardiac amyloidosis (middle row and bottom row). In the upper row, the patient with no cardiac amyloidosis has no LGE and normal native T1 and ECV maps; in the middle row, the patient with cardiac amyloidosis has subendocardial LGE, elevated T1 values, and elevated ECV values; in the bottom row, the patient with cardiac amyloidosis has a high cardiac amyloid load, with transmural LGE, high native T1 values, and high ECV values.

and endomyocardial biopsy. In addition, the utility of these agents in identifying ATTR-CM before increases in wall thickness are observed or electrocardiographic voltage is reduced<sup>15,41,44,45</sup> suggests that they may be useful for early identification of affected individuals. Molecular imaging with targeted amyloid-binding positron emission tomography radiotracers <sup>11</sup>C-Pittsburgh compound B (<sup>11</sup>C-PIB), <sup>18</sup>F-florbetapir, and <sup>18</sup>F-florbetaben is an emerging quantitative diagnostic approach that may distinguish cardiac amyloidosis from other forms of heart disease.<sup>46–49</sup>

## DIAGNOSIS AND ASSESSMENT

A diagnostic approach for patients with suspected cardiac amyloidosis should include testing for monoclonal protein followed by scintigraphy or biopsy (Figure 6).<sup>50</sup> Clinicians should note that up to 40% of patients with ATTR-CA can have a monoclonal gammopathy of unknown significance<sup>51</sup> and in this setting scintigraphy alone cannot ensure a diagnosis with 100% specificity. Nuclear imaging can also be performed concurrent to AL assessment, even in the case of a detected

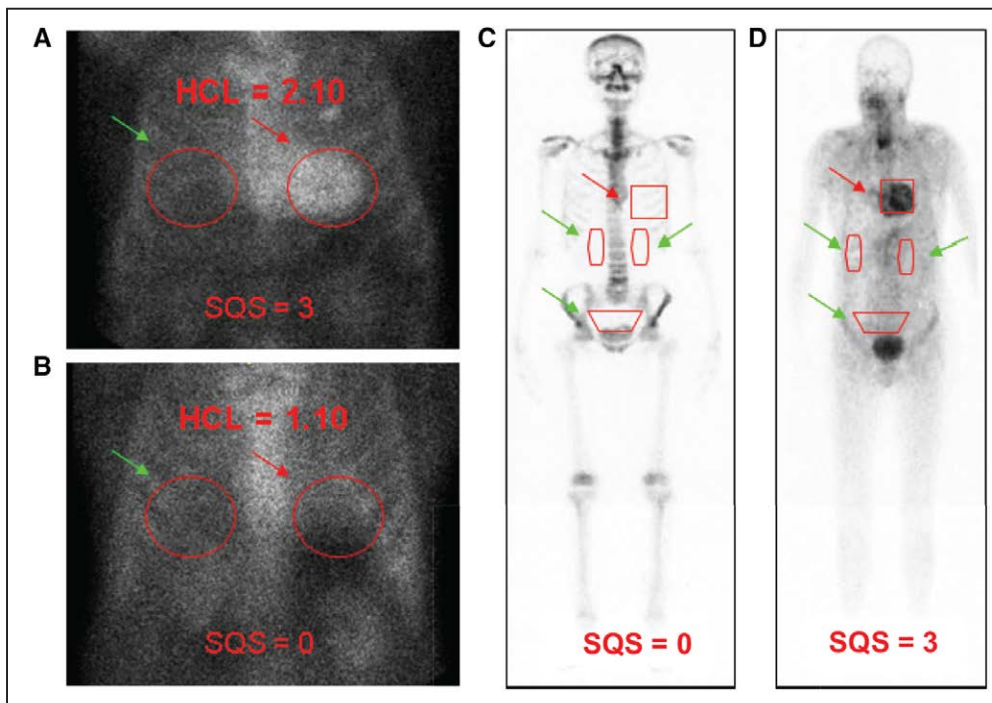


**Figure 4.** <sup>99m</sup>Tc imaging procedures for cardiac amyloidosis.

SPECT imaging to identify myocardial retention of technetium-based isotopes is particularly useful in discriminating blood pool on planar scans that result in a false-positive test from myocardial uptake of the isotope indicative of transthyretin amyloidosis with cardiomyopathy. <sup>99m</sup>Tc-pyrophosphate imaging for transthyretin cardiac amyloidosis. Adapted with permission of the American Society of Nuclear Cardiology. ©2018, American Society of Nuclear Cardiology.

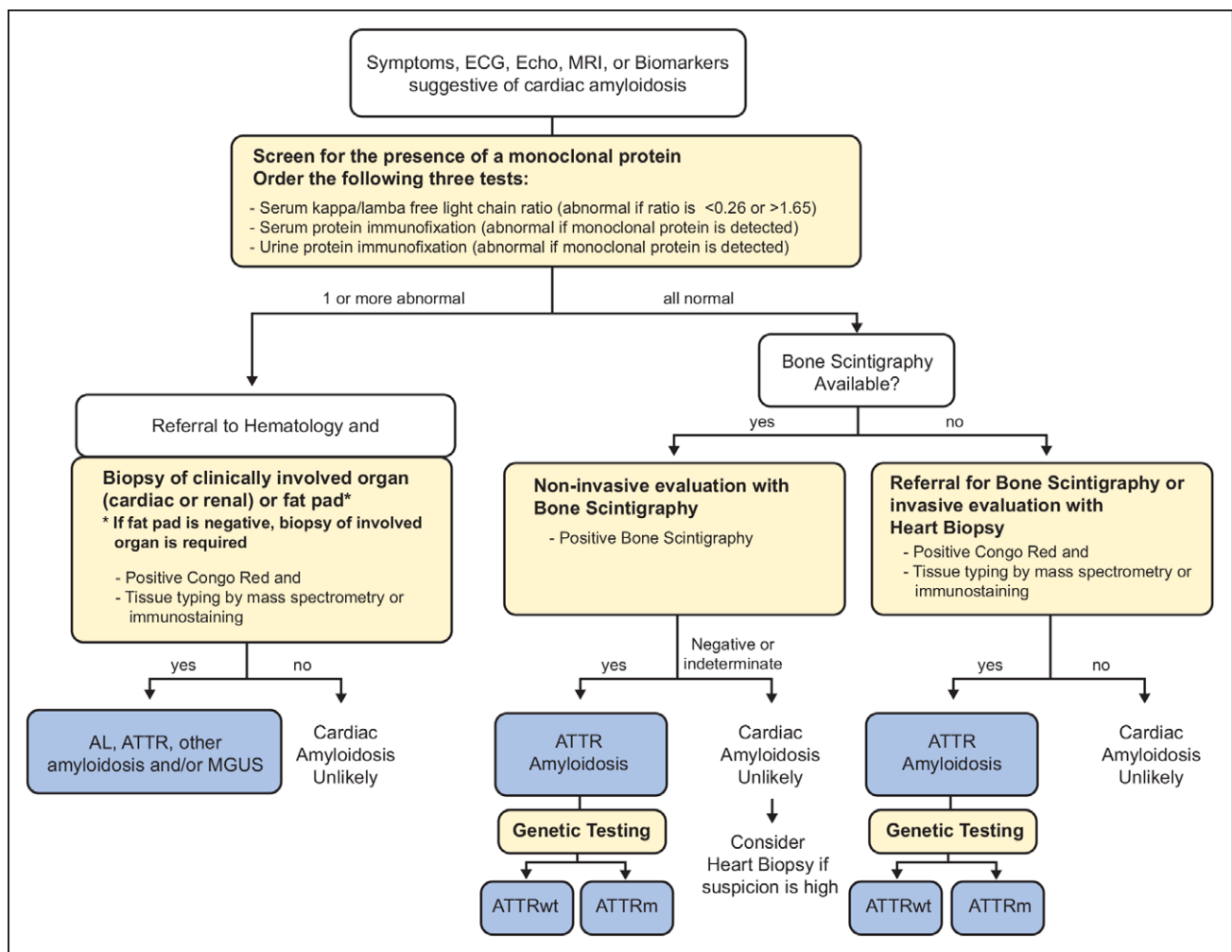
monoclonal gammopathy, for additive information. However, in the context of monoclonal gammopathy of unknown significance, endomyocardial biopsy is necessary to definitively diagnose ATTR-CM. If no monoclonal protein is detected and a diagnosis of AL cardiac amyloidosis is excluded, radionuclide scintigraphy alone, without myocardial biopsy, can be used to diagnose ATTR-CM.<sup>37</sup> Among all radiotracers that have been tested, diphosphono-1,2-propanodicarboxylic

acid, pyrophosphate, and hydroxymethylene diphosphonate are recommended for the diagnosis of amyloidosis (Table 2).<sup>52,53</sup> The radiotracer <sup>123</sup>I-metaiodobenzylguanidine can detect sympathetic innervation of the heart and may indicate cardiac amyloid,<sup>63-66</sup> although <sup>123</sup>I-metaiodobenzylguanidine imaging is also abnormal in other cardiac conditions and is not specific enough to diagnose ATTR-CM. If ATTR-CM is identified, TTR genotyping should be performed.



**Figure 5.** Semiquantitative approach to <sup>99m</sup>Tc-PYP/DPD/HMDP imaging in cardiac amyloidosis.

Semiquantitative methods to generate heart-to-contralateral (HCL) ratios with a target region of interest (ROI) over the heart (A, B, red arrows) mirrored over the contralateral chest for a background ROI (A, B, green arrows). An HCL ratio of >1.5 on 1-h imaging is diagnostic of transthyretin amyloidosis with predominant cardiomyopathy (ATTR-CM). Comparatively, <sup>99m</sup>Tc DPD includes a whole-body scan, 25 to 30 mCi of radiotracer, 200 min of study time, with heart-to-whole-body ratios generated by a target ROI over the heart (C, D, red arrows) as well as background ROIs over the kidneys and bladder (C, D, green arrows). C and D, Adapted from Perugini et al<sup>39</sup> with permission. Copyright ©2005, Journal of the American College of Cardiology. <sup>99m</sup>Tc hydroxymethylene diphosphonate was validated for diagnosing ATTR CA, and representative scans show diffuse myocardial uptake in a patient with cardiac transthyretin amyloidosis at baseline. <sup>99m</sup>Tc-DPD indicates <sup>99m</sup>technetium-3,3-diphosphono-1,2-propanodicarboxylic acid; <sup>99m</sup>Tc-HMDP, hydroxymethylene diphosphonate; <sup>99m</sup>Tc-PYP, technetium pyrophosphate.



**Figure 6. Diagnostic algorithm for patients with suspected cardiac amyloidosis.**

Note that urine protein electrophoresis with immunofixation can be performed on spot or 24-h urine collection. AL indicates light chain amyloidosis; ATTR, transthyretin amyloidosis; ATTRm, mutant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; ECG, electrocardiography; Echo, echocardiogram; MGUS, monoclonal gammopathy of undetermined significance; MRI, magnetic resonance imaging. Adapted from Nativi-Nicolau and Maurer<sup>50</sup> with permission. Copyright ©2018, Wolters Kluwer Health, Inc.

If monoclonal protein is detected, assessments should include amyloid typing of a tissue biopsy from a clinically affected organ (eg, endomyocardial biopsy if the heart is clinically affected), abdominal fat, or bone marrow, depending on availability and expertise at the clinic. TTR genotyping should be performed if a diagnosis of ATTR amyloidosis is made on biopsy. Endomyocardial biopsy is invasive, carries a small risk for serious complications, and requires technical expertise, whereas fat pad biopsy is less invasive and poses little risk but has varying sensitivity in ATTR-CM (with roughly 45% sensitivity for ATTRm and roughly 15% sensitivity for ATTRwt).<sup>67</sup> Given the high false-negative rate from biopsies of nonclinically involved sites (eg, fat pad, bone marrow), further evaluation is warranted even in the presence of a negative biopsy from such sites if clinical suspicion remains elevated. In such cases, biopsy of a clinically affected organ (eg, endomyocardial biopsy) is imperative. Endomyocardial biopsy assessment with Congo red staining has ≈100% specificity and sensitivity for detecting amyloid deposits

and is still considered the gold standard in situations with equivocal noninvasive findings.<sup>68</sup> Regardless of the site of biopsy, amyloid deposits must then undergo either immunofluorescence or mass spectrometry to confirm the amyloidosis subtype (eg, AL or ATTR).

In patients with confirmed ATTR amyloidosis, TTR gene sequencing is necessary even if they do not have a family history of amyloidosis or evidence of polyneuropathy because the penetrance of ATTRm varies among the variants and families. If a TTR variant is detected, genetic counseling for relatives of the affected patient is indicated.

## Prognostic Stratification Using Biomarkers

Natriuretic peptides and cardiac troponins, though not specific markers of ATTR-CM, are well established to assess risk (eg, Mayo staging) and to evaluate response to treatment in patients with AL amyloidosis.<sup>69–71</sup> However, evidence in AL amyloidosis may not apply to ATTR



**Table 2. Radiotracers for Imaging of Cardiac Amyloidosis**

Radiotracer	Imaging Modality	Mechanism of Uptake	Amyloid Subtype Uptake	Imaging Capability	Considerations
Bone avid tracers primarily used in the United States					
<sup>99m</sup> Tc-PYP <sup>44,54-57</sup>	Planar/SPECT	Bone tracer	ATTR-CM	Diagnostic; possibly early detection	Some uptake in patients with AL amyloidosis, less than ATTR amyloidosis
Bone avid tracers primarily used outside the United States					
<sup>99m</sup> Tc-DPD <sup>39-41</sup> and <sup>99m</sup> Tc-HMDP <sup>38,58,59</sup>	Planar/SPECT	Bone tracer	ATTR-CM	Diagnostic; possibly early detection and disease monitoring	Some uptake in patients with AL amyloidosis, less than ATTR amyloidosis
Amyloid-binding radiotracers					
<sup>11</sup> C-PIB <sup>47,60,61</sup>	PET	Amyloid deposits	ATTR-CM, AL amyloidosis	Possibly quantitation of amyloid burden, disease monitoring	Short half-life, expensive isotope relative to SPECT tracers
<sup>18</sup> F-florbetapir <sup>48,62</sup>	PET	Amyloid deposits	ATTR-CM, AL amyloidosis	Possibly early detection, quantitation, and disease monitoring	Expensive isotope relative to SPECT tracers
<sup>18</sup> F-florbetaben <sup>49</sup>	PET	Amyloid deposits	ATTR-CM, AL amyloidosis	Possibly early detection, quantitation, and disease monitoring	Expensive isotope relative to SPECT tracers
<sup>18</sup> F-NaF <sup>52,53</sup>	PET	Bone tracer	Equivocal ATTR-CM	Possibly early detection, quantitation, and disease monitoring	No uptake in patients with AL amyloidosis, equivocal uptake in patients with ATTR-CM

The tracers <sup>99m</sup>Tc-MDP and <sup>99m</sup>Tc-aprotinin are not recommended. <sup>11</sup>C-PIB indicates Pittsburgh compound B; <sup>18</sup>F-NaF, sodium fluoride; <sup>99m</sup>Tc-DPD, <sup>99m</sup>technetium-3,3-diphosphono-1,2-propanodicarboxylic acid; <sup>99m</sup>Tc-HMDP, hydroxymethylene diphosphonate; <sup>99m</sup>Tc-PYP, technetium pyrophosphate; <sup>123</sup>I, iodine-123; AL, amyloid light chain; ATTR-CM, transthyretin amyloidosis with predominant cardiomyopathy (either wild-type or hereditary); PET, positron emission tomography; and SPECT, single-photon emission computed tomography.

amyloidosis because the 2 diseases have substantially different biologies.<sup>29,72,73</sup> Different staging systems for ATTRwt amyloidosis and ATTR-CM have been proposed. A proposed system in patients with ATTRwt includes NT-proBNP (>3000 pg/mL) and troponin T (>0.05 ng/mL).<sup>74</sup> The most recently proposed system for staging ATTR-CM (including ATTRwt and ATTRm) uses NT-proBNP (>3000 pg/mL) and estimated glomerular filtration rate (<45 mL/minute).<sup>75</sup> Staging in both systems is defined such that stage 1 does not meet either threshold, stage 2 meets 1 of the 2 thresholds, and stage 3 meets both thresholds.

## FUTURE DIRECTIONS

To reduce the delays in diagnosis of this important health problem, specific programs for screening or early identification should be studied that leverage techniques having appropriate sensitivity and specificity as well as favorable cost/benefit. Implementation of appropriate screening programs for ATTR-CM will need to include factors such as whether there are methods and facilities available for diagnosis, whether certain diagnostic tests are acceptable to those at risk, and the particular test characteristics, as well as cost and benefits of treatments and when appropriate timing would be for the intervention. Given that prognosis is highly dependent on the underlying cardiac dysfunction coupled with the recently available treatments for ATTR amyloidosis, screening programs may become important.

## CONCLUSIONS

ATTR amyloidosis is a progressive disease associated with increased morbidity and mortality and occurs in inherited (ATTRm or hereditary ATTR) or acquired (ATTRwt) forms. Disease-related cardiac dysfunction in patients with ATTR amyloidosis is associated with particularly poor outcomes and is a manifestation of many of the genetic variants and the wild-type form of ATTR amyloidosis.

Diagnosis of ATTR-CM is often missed or mistaken as hypertrophic cardiomyopathy or heart failure with preserved ejection fraction of unknown cause. Although considered a rare disease, the true prevalence of ATTR-CM is unclear and is likely higher than appreciated. Physicians should consider systemic signs and symptoms along with evidence from biomarkers and imaging to build suspicion for ATTR-CM. To facilitate early diagnosis of ATTR-CM, evaluation of myocardial uptake on bone scintigraphy should be considered in patients with HF, unexplained neuropathy, family history of amyloidosis, or unexplained increased LV wall thickness. Appropriate evidence on echocardiography or cardiac MRI—combined with no light chain clone, grade ≥2 myocardial uptake of <sup>99m</sup>Tc-pyrophosphate, diphosphono-1,2-propanodicarboxylic acid, and hydroxymethylene diphosphonate—is diagnostic of ATTR-CM, in which case endomyocardial biopsy is unnecessary. Genetic testing should be performed to differentiate ATTRm from ATTRwt causes of ATTR-CM.



The consensus recommendations described in this review were developed with the goal of providing clinicians with an overview of key aspects of ATTR-CM diagnosis. We hope these recommendations facilitate early, rapid, and accurate identification of ATTR-CM to allow implementation of targeted, disease-modifying treatment and improved outcomes for patients.

## ARTICLE INFORMATION

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