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Multisocietal Expert Consensus
RECOMMENDATIONS

Including 2021 Addendum

A Summary of Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis

INCLUDING ADDENDUM PUBLISHED IN JULY 2021

Adapted from ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI* Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Evidence Base and Standardized Methods of Imaging and Diagnostic Criteria and Appropriate Utilization, Parts 1 and 2, including 2021 addendum

*The consensus report was written by a writing group of experts in cardiovascular imaging and amyloidosis assembled by the American Society of Nuclear Cardiology and endorsed by 8 societies including the American College of Cardiology, American Heart Association, American Society of Echocardiography, European Association of Nuclear Medicine, Heart Failure Society of America, International Society of Amyloidosis, Society of Cardiovascular Magnetic Resonance, and Society of Nuclear Medicine and Molecular Imaging.[1,2]

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Standardizing the Diagnostic Multimodality Cardiac Amyloidosis Imaging Approach[1]

The standardization for using echocardiography (echo), cardiac magnetic resonance (CMR), and radionuclide imaging in the evaluation of cardiac amyloidosis is an unmet need that could potentially increase diagnosis and improve quality of care and patient outcomes for this highly morbid, underdiagnosed disease.

Cardiac amyloidosis is a group of diseases that is life-threatening and remains largely underrecognized or delayed in diagnosis due to many factors, and there is a lack of clear diagnostic imaging guidelines

Despite an abundance of noninvasive cardiac imaging options for the evaluation of cardiac amyloidosis, there is a lack of consensus on their clinical utility, which is problematic considering the importance of early diagnosis

In response, a group of experts in cardiovascular imaging and amyloidosis established an international consensus report to guide the appropriate clinical utilization of imaging in cardiac amyloidosis; an addendum to these guidelines was published in 2021

KEY POINTS, INCLUDING RECENT UPDATES, FROM MULTISOCIETAL EXPERT CONSENSUS RECOMMENDATIONS (MECR)[1]*

Evidence
on the effectiveness of echo, CMR, and radionuclide imaging in the screening, diagnosis, and management of cardiac amyloidosis

Defined, standardized protocols
for the gathering, analysis, and reporting of these noninvasive imaging techniques in the assessment of cardiac amyloidosis

Consensus on diagnostic criteria
for cardiac amyloidosis, identifying clinical indications and providing recommendations on appropriate utilization in these clinical scenarios

*Cardiac amyloidosis, including both immunoglobulin light chain amyloid fibril protein (AL) and transthyretin amyloid fibril protein (ATTR) types.[1]

THE NEED FOR A MULTIMODAL APPROACH

No existing noninvasive tools can individually diagnose cardiac amyloidosis or confirm etiologic subtype, **which necessitates a multimodal cardiac imaging approach** that includes[1]:

Raising suspicion

- **Echo** to assess **structure and function**, frequently used in patients with concerning cardiac symptoms
- **CMR** to provide **tissue characterization** as well as high-resolution morphologic and functional assessment, while also offering differentiation of cardiac amyloidosis from other cardiomyopathies and potentially early detection of cardiac amyloidosis

Reaching a definitive diagnosis

- **Radionuclide (^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP)* imaging** to assist in the **noninvasive diagnosis** of transthyretin amyloid cardiomyopathy (ATTR-CM) with high sensitivity and specificity when combined with testing to rule out AL

Cardiac amyloidosis is a cardiomyopathy resulting from the myocardial accumulation of misfolded protein deposits, or amyloid fibrils.

Cardiac amyloidosis most commonly results from 1 of the following 2 protein precursors:

- AL—amyloid fibrils form from misfolded monoclonal immunoglobulin light chain protein produced by bone marrow plasma cells
- ATTR—amyloid fibrils form from misfolded transthyretin (TTR), a serum transport protein for thyroid hormone and retinol that is synthesized primarily by the liver

Exclusion of a monoclonal process with serum/urine immunofixation and a serum free light chain assay in all patients with suspected amyloidosis is critical.[1]

*Only approved radiotracer can be used.

^{99m}Tc-DPD, ^{99m}technetium-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc-HMDP, ^{99m}technetium-labeled hydroxymethylene diphosphonate; ^{99m}Tc-PYP, ^{99m}technetium-labeled pyrophosphate.

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Echocardiography

Echocardiography (Echo) as a Cardiac Imaging Modality

BASIS OF EVIDENCE

Echo plays a major role in the noninvasive diagnosis of cardiac amyloidosis due to its wide availability and capacity to assess **structure and function**.[1]

Cardiac amyloidosis is suggested on echo when[1]:

- Morphological findings related to amyloid infiltration show **increased left ventricular (LV) wall thickness** (>1.2 cm) and **increased LV mass** in the absence of any other plausible causes of LV hypertrophy
- **Increased echogenicity of the myocardium** (sparkling) is identified in conjunction with severely reduced longitudinal LV function
- Any of the following echocardiographic findings are present:
  - Normal to small LV cavity size
  - Biatrial enlargement and dysfunction
  - Left atrial (LA) and LA appendage stasis and thrombi
  - Thickened valves
  - Right ventricular and interatrial septal thickening
  - Pericardial effusion
  - Tissue Doppler imaging (TDI) <5 cm/s
- Results indicate **impaired LA reservoir and pump functions**, possibly resulting in the formation of atrial and atrial appendage thrombi
- **Presence of discordance of QRS voltage to echocardiographic LV wall thickness**
- On speckle-tracking echocardiography (STE), a pattern of **reduced longitudinal shortening with preserved LV ejection fraction** and radial shortening can be seen
  - STE can differentiate cardiac amyloidosis from other causes of increased LV wall thickness
  - STE can also refine the noninvasive recognition of disease by quantitating longitudinal systolic function
  - A pattern of distribution of STE-derived longitudinal strain in which basal LV segments are severely impaired while apical segments are relatively spared is commonly observed in patients with cardiac amyloidosis

Echocardiography
PROS AND CONS[1]

Pros

- Portability, bedside availability, widely available
- Superior diastolic function assessment
- A critical component of the diagnostic evaluation and management of patients with cardiac amyloidosis

Cons

- Not sufficient to diagnose cardiac amyloidosis on its own
- Lacks tissue characterization provided by cardiovascular magnetic resonance (CMR)
- Cannot distinguish immunoglobulin light chain amyloidosis (AL) from transthyretin amyloid cardiomyopathy (ATTR-CM), requiring evaluation to exclude AL and further imaging studies to definitively diagnose ATTR-CM

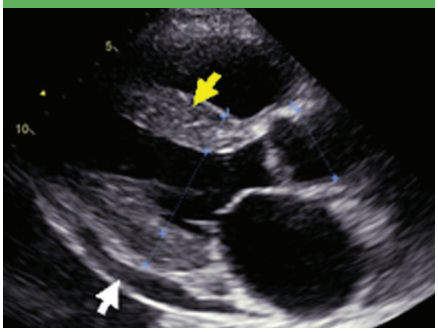
Echocardiography (Echo) as a Cardiac Imaging Modality *continued*

KEY RECOMMENDATIONS FOR THE ROLE OF ECHO WHEN CARDIAC AMYLOIDOSIS IS SUSPECTED[1]

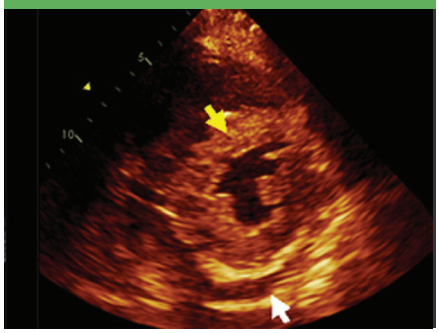
- Perform comprehensive 2D echo, including quantitative TDI and STE, in all patients with unexplained LV wall thickening and a clinical suspicion of cardiac amyloidosis
- Any echocardiographic abnormalities suggestive of cardiac amyloidosis should prompt further evaluation
- Combine echocardiographic parameters with electrocardiographic, clinical, biomarker, and other imaging findings to maximize diagnostic accuracy

CARDIAC AMYLOIDOSIS ON ECHO[1] (PART 1)

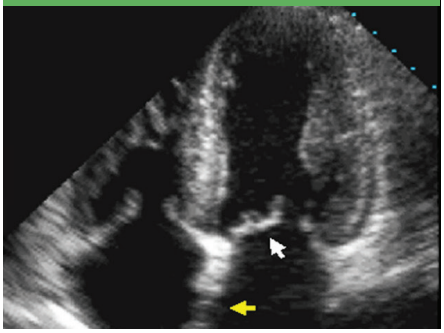
A Parasternal long axis



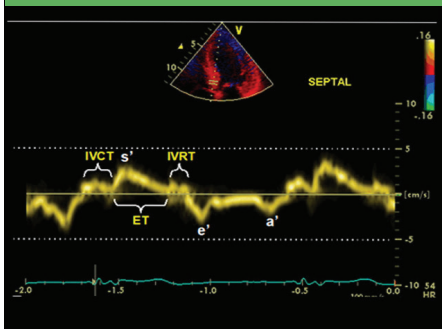
B Parasternal short axis



C Apical 4-chamber view



D Tissue Doppler imaging



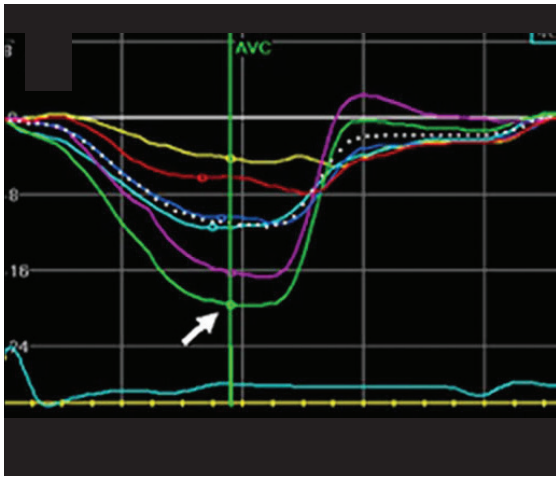
Characteristic Appearance With 2D Echocardiography

(**a**) (parasternal long axis) and (**b**) (parasternal short axis) demonstrate increased LV wall thickness with a sparkling texture of the myocardium (yellow arrows) in a patient with primary (AL) cardiac amyloidosis. Also, note the small pericardial effusion (white arrows), which is often seen in patients with cardiac amyloidosis. (**c**) (apical 4-chamber view) demonstrates increased biventricular wall thickness, biatrial enlargement, and increased thickening of the interatrial septum (yellow arrow) and mitral valve leaflets (white arrow) in a patient with wtATTR-CM. (**d**) TDI tracing taken at the septal mitral annulus in a patient with ATTR-CM. The TDI tracing shows the "5-5-5" sign (*s*′ [systolic], *e*′ [early diastolic], and *a*′ [late (atrial) diastolic] tissue velocities are all <5 cm/s), which is seen in patients with more advanced cardiac amyloidosis. The dotted lines denote the 5 cm/s cutoff for systolic and diastolic tissue velocities. In addition to the decreased tissue velocities, isovolumic contraction and relaxation times (IVCT and IVRT, respectively) are increased and ejection time (ET) is decreased, findings also seen in patients with cardiac amyloidosis, especially as the disease becomes more advanced.

Echocardiography (Echo) as a Cardiac Imaging Modality *continued*

CARDIAC AMYLOIDOSIS ON ECHO[1] (PART 2)

A



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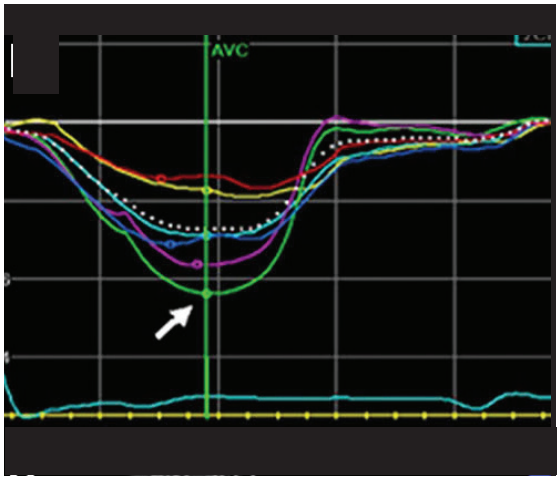
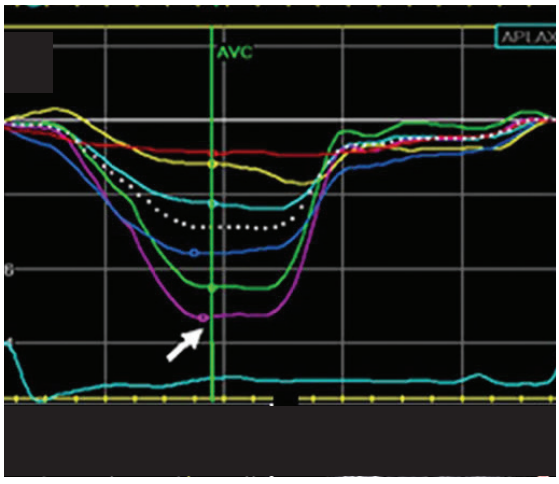
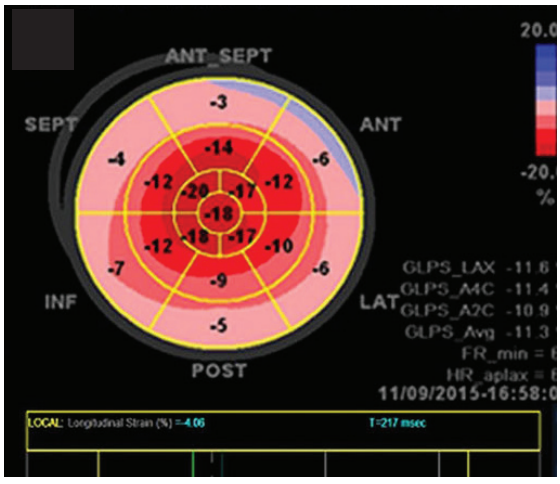


C



D



LV Longitudinal Strain Abnormalities

(**a**) (apical 4-chamber view), (**b**) (apical 2-chamber view), (**c**) (apical 3-chamber view) all show abnormal longitudinal strain in the basal and mid segments with relative preservation in the apical segments (purple and green curves, white arrows) in a patient with hATTR-CM, (**d**) shows the corresponding bull's-eye map of the longitudinal strain pattern throughout the left ventricle with the "cherry-on-the-top" sign (red denotes normal longitudinal strain at the apex and pink/blue denotes abnormal longitudinal strain at the mid/basal left ventricle).

Echocardiography (Echo) as a Cardiac Imaging Modality *continued*

STANDARDIZED ACQUISITION, INTERPRETATION, AND REPORTING OF ECHO FOR CARDIAC AMYLOIDOSIS[1] (PART 1)

Parameter for acquisition and reporting	Abnormal parameter	Notes	Recommendations for reporting
2D, Color, and Spectral Doppler Imaging			Required
LV wall thickness	Increased LV wall thickness (>1.2 cm) and increased relative wall thickness (>0.42)	Increased LV wall thickness relative to ECG QRS voltage is particularly suggestive	Required
Myocardial echogenicity	Increased echogenicity of the myocardium (sparkling, hyper-refractile "texture" of the myocardium)	Not highly specific (differential diagnosis includes ESRD or other infiltrative cardiomyopathies). However, this finding in conjunction with severely reduced longitudinal function of the LV is highly suggestive	Required
Atrial size and function	Atrial enlargement and dysfunction	Nonspecific but important finding to support the diagnosis and potentially provide insight into risk for stroke or arterial embolism	Required
Interatrial septum and valves	Thickening of the interatrial septum and valves (>0.5 cm)	Nonspecific, but suggestive of the diagnosis	Required
Pericardial effusion	Pericardial effusion	Nonspecific, but when coupled with other echo signs is suggestive of the diagnosis	Required
Diastolic function	Grade 2 or worse diastolic dysfunction with high E/A ratio (>1.5) and reduced E deceleration time (<150 ms)	Doppler diastolic function is helpful in determining prognosis. Severely reduced A wave velocity can be due to LA failure, which can be helpful in determining risk of stroke	Required
Estimated PA systolic and right atrial pressure	Increased pressures (>35 mm Hg for PA, ≥10 mm Hg for RA)	These are important parameters to estimate volume status and optimize diuretic dosing	Required
Tissue Doppler Imaging			Required
Tissue Doppler velocities	Reduced tissue Doppler *s'*, *e'*, and *a'* velocities (all <5 cm/s)	If present, the "5-5-5" sign (all TDI velocities <5 cm/s) can be useful and is typically highly suggestive of the diagnosis but may not be sensitive for the diagnosis in early forms of the disease	Required

Echocardiography (Echo) as a Cardiac Imaging Modality *continued*

STANDARDIZED ACQUISITION, INTERPRETATION, AND REPORTING OF ECHO FOR CARDIAC AMYLOIDOSIS[1] (PART 2)

Parameter for acquisition and reporting	Abnormal parameter	Notes	Recommendations for reporting
Strain Imaging			Recommended
Longitudinal LV strain	Decreased global longitudinal LV strain (absolute value less than -15%)	2D and STE shows characteristic appearance of myocardial deformation in patients with cardiac amyloidosis	Recommended
Longitudinal LV strain bull's-eye map	"Cherry-on-the-top" sign on STE longitudinal strain bull's-eye map (preservation of apical longitudinal strain with severely abnormal basal and mid-LV longitudinal strain)	Characteristic bull's-eye pattern is likely the most specific sign to rule in the diagnosis of cardiac amyloidosis (but still does not differentiate ATTR vs AL amyloidosis)	Recommended
REPORTING OF ECHO FINDINGS IN CARDIAC AMYLOIDOSIS			
An overall interpretation of the echo findings into categories of: ● **Not suggestive:** Normal LV wall thickness, normal LV mass, normal atrial size, septal or lateral tissue Doppler *e'* velocity >10 cm/s ● **Strongly suggestive:** Increased LV wall thickness, increased LV mass, typical LV longitudinal strain pattern, mitral annular TDI <5 cm/s, biatrial enlargement, small A wave in sinus rhythm, small pericardial and/or pleural effusions ● **Equivocal:** Findings not described above			Required
Interpret the echo results in the context of prior evaluation			Recommended
Provide follow-up recommendations: • Strongly suggestive echo findings cannot distinguish AL from ATTR-CM • Endomyocardial biopsy (EMB) is not always indicated in patients with strongly suggestive echo findings. Please see "Expert Consensus Recommendations for Diagnosis of Cardiac Amyloidosis" on last page for indications for EMB • Consider evaluation (1) to exclude AL amyloidosis, evaluate for plasma cell dyscrasia (serum/urine immunofixation, serum free light chain [SFLC] assay) and (2) to exclude ATTR-CM, consider imaging with ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP			Recommended

^{99m}Tc-DPD, ^{99m}technetium-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc-HMDP, ^{99m}technetium-labeled hydroxymethylene diphosphonate; ^{99m}Tc-PYP, ^{99m}technetium-labeled pyrophosphate.

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Cardiac Magnetic Resonance

Cardiac Magnetic Resonance (CMR) as a Cardiac Imaging Modality for Cardiac Amyloidosis

BASIS OF EVIDENCE

CMR may raise suspicion of disease in 2 scenarios[1]:

1. Differentiation between cardiac amyloidosis and other cardiomyopathic conditions with increased wall thickening
2. Detection of early cardiac involvement in patients presenting with symptoms of systemic amyloidosis

In addition to high-resolution morphologic and functional assessment, CMR is able to provide tissue characterization.[1]

Cardiac amyloidosis is suggested on CMR when the following are observed[1]:

- Functional and morphologic assessment:
  - Increased left ventricular (LV) wall thickness, increased LV mass, biatrial enlargement, pericardial effusion, low stroke volume index, increased atrial volume, reduced atrial function, and reduced LV function in advanced cases
- Tissue characterization:
  - Late gadolinium enhancement (LGE) assessment: abnormal diffuse or global LGE patterns, including subendocardial LGE, patchy LGE, difficulty in achieving myocardial nulling over a range of inversion times, and dark blood pool signal
  - Abnormal myocardial signal suppression pattern
  - T1 mapping post-contrast: extracellular volume (ECV) >0.40

CMR
PROS AND CONS[1,3]

Pros

- CMR may be advantageous in the following scenarios if echocardiographic acoustic windows are poor:
  - To characterize the right ventricle
  - To characterize tissue based on the contrast-enhanced patterns of myocardial infiltration
  - To precisely quantify cardiac chamber volumes and ventricular mass

Cons

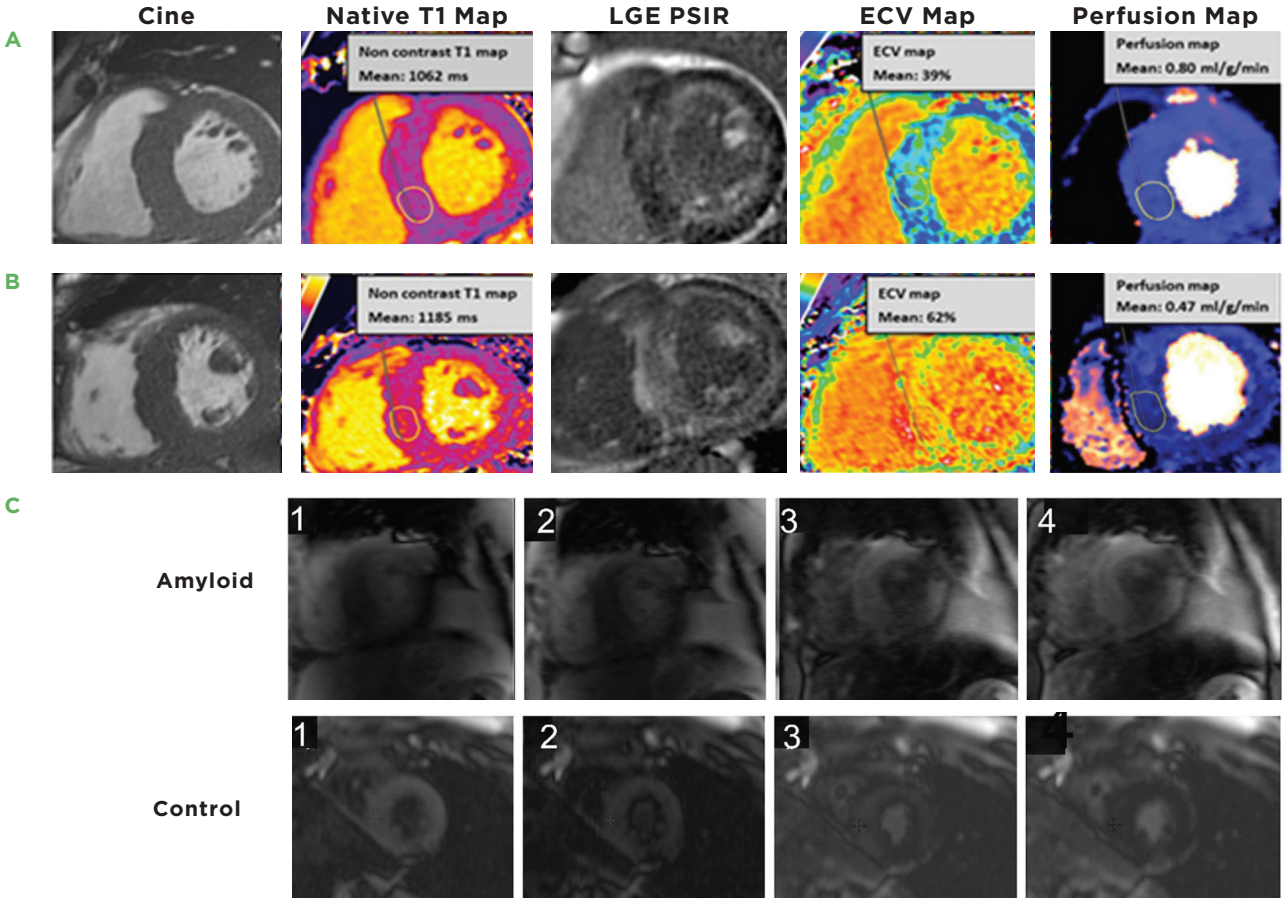
- Cannot distinguish immunoglobulin light chain amyloidosis (AL) from transthyretin amyloid cardiomyopathy (ATTR-CM), requiring evaluation to exclude AL and further imaging studies to definitively diagnose ATTR-CM
- CMR with LGE may be contraindicated in patients with ATTR-CM who have concurrent renal dysfunction
- Restricted to specialty locations and requires specialty equipment and expertise
- Contraindicated with some pacemakers and other implanted hardware
- Long test compared with other imaging modalities
- Some patients may experience claustrophobia

Cardiac Magnetic Resonance (CMR) as a Cardiac Imaging Modality for Cardiac Amyloidosis *continued*

KEY RECOMMENDATIONS FOR THE ROLE OF CMR WHEN CARDIAC AMYLOIDOSIS IS SUSPECTED[1]

- Comprehensive CMR-based evaluation of cardiac structure, function, and myocardial tissue characterization
- In patients with biopsy-proven systemic amyloidosis, typical CMR findings should be combined with structural findings of increased wall thickness and myocardial mass to diagnose cardiac involvement
  - Typical CMR features should prompt further evaluation for cardiac amyloidosis in the absence of documented systemic amyloidosis
- CMR does not definitively distinguish AL from ATTR-CM
- To maximize diagnostic accuracy, CMR parameters should be combined with electrocardiographic, clinical, biomarker, and other imaging findings

CARDIAC AMYLOIDOSIS ON CMR[1]



Characteristic Appearance

Two patients [upper and lower row, (**a**) and (**b**)] with cardiac amyloidosis: similar mass (cine), but significantly different amyloid burden, with the patient at the bottom (**b**) showing a significant higher amyloid burden (higher native T1, higher ECV, transmural LGE) and lower myocardial resting perfusion (also, after adjusting for ECV expansion). (**c**) Inversion scout images in 2 patients, upper row amyloid, lower row nonamyloid control. These images show a distinct pattern of myocardial and blood pool nulling. In the nonamyloid subject, the blood pool nulls prior to myocardium; in contrast, in the subject with cardiac amyloidosis, the myocardium nulls prior to the blood pool.

PSIR, phase-sensitive inversion recovery.

Cardiac Magnetic Resonance (CMR) as a Cardiac Imaging Modality for Cardiac Amyloidosis *continued*

RECOMMENDATIONS FOR STANDARDIZED INTERPRETATION AND REPORTING OF CMR FOR CARDIAC AMYLOIDOSIS[1] (PART 2)

Parameter for acquisition and reporting	Criteria	Notes	Recommendations for reporting
Myocardial signal suppression pattern	Abnormal myocardial signal suppression pattern Myocardium nulls before blood pool on Look-Locker, Cine IR, or TI scout sequences		Recommended
Amyloid Quantitation			
Native T1 mapping (pre-contrast)	Abnormal T1 mapping (criteria may vary based on the sequence used [MOLLI, ShMOLLI] and the field strength of the magnet)	Assess interstitial amyloid accumulation without gadolinium Reference range should be based on a site's local calibrated values on specific field strengths	Recommended
T1 mapping post-contrast (ECV estimation)	ECV >0.40 is highly suggestive of cardiac amyloidosis	Assess expansion of ECV from interstitial amyloid accumulation A. 1 pre- and 1 post-contrast measurement (15-minute post-contrast injection) B. 1 pre- and 3 post-contrast measurements (5-, 15-, and 25-minutes post-contrast injection)	A. Recommended B. Optional

REPORTING OF CMR FINDINGS IN CARDIAC AMYLOIDOSIS	
An overall interpretation of the CMR findings into categories of: • **Not suggestive:** Normal LV wall thickness, normal LV mass, no ventricular LGE, normal atrial size • **Strongly suggestive:** Increased LV wall thickness, increased LV mass, biatrial enlargement, typical diffuse or global LGE pattern, difficulty achieving myocardial nulling, significantly increased ECV (>0.40), small pericardial and/or pleural effusions • **Equivocal:** Findings not described above	Required
Interpret the CMR results in the context of prior evaluation	Recommended
Provide follow-up recommendations: Strongly suggestive CMR findings cannot distinguish AL from ATTR-CM Endomyocardial biopsy is frequently unnecessary in patients with strongly suggestive CMR findings and histologically defined systemic amyloidosis or diagnostic ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP imaging Consider evaluation (1) to exclude AL amyloidosis, evaluate for plasma cell dyscrasia (serum/urine immunofixation, serum free light chain [SFLC] assay) and (2) to exclude ATTR-CM, consider imaging with ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP	Recommended

T2 mapping is currently not part of the standard clinical amyloidosis imaging protocol
^{99m}Tc-DPD, ^{99m}technetium-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc-HMDP, ^{99m}technetium-labeled hydroxymethylene diphosphonate; ^{99m}Tc-PYP, ^{99m}technetium-labeled pyrophosphate; ShMOLLI, shortened modified Look-Locker inversion recovery.

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Radionuclide Imaging (^{99m}Tc-PYP/ ^{99m}Tc-DPD/^{99m}Tc-HMDP)

^{99m}Tc-DPD, ^{99m}technetium-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc-HMDP, ^{99m}technetium-labeled hydroxymethylene diphosphonate; ^{99m}Tc-PYP, ^{99m}technetium-labeled pyrophosphate.

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Radionuclide Imaging (^{99m}Tc-PYP/ ^{99m}Tc-DPD/^{99m}Tc-HMDP)

^{99m}Tc-DPD, ^{99m}technetium-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc-HMDP, ^{99m}technetium-labeled hydroxymethylene diphosphonate; ^{99m}Tc-PYP, ^{99m}technetium-labeled pyrophosphate.

^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP Radionuclide Imaging as a Diagnostic Modality*

BASIS OF EVIDENCE

Radionuclide imaging with technetium-labeled bone-avid radiotracers can definitively and noninvasively diagnose transthyretin amyloid cardiomyopathy (ATTR-CM) once immunoglobulin light chain amyloid fibril protein (AL) is ruled out.[1†]

- Scintigraphy with ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP provides a unique myocardial uptake pattern in amyloid[1]
- Studies comparing ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP scintigraphy with endomyocardial biopsy (EMB) found that bone radiotracers have avidity for ATTR-CM deposits, whereas avidity for AL cardiac amyloid deposits is minimal or absent[1]
- A variety of bone-avid radiotracers like ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP compounds can diagnose ATTR-CM[1]
  - A multicenter international study of scintigraphy at amyloid centers of excellence demonstrated 100% specificity for ATTR-CM using visual grade 2 or 3 with concurrent testing to rule out AL[4‡§]
  - ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP may also detect extracardiac (skeletal muscle and lung) amyloid infiltration[1]
- Both planar and single-photon emission computed tomography (SPECT) imaging should be reviewed and interpreted using visual and semiquantitative approaches[1]
  - SPECT imaging is necessary for studies that show planar myocardial uptake because it can help differentiate myocardial uptake from blood pool or overlying bone uptake[1]
- Cardiac scintigraphy with bone-avid radiotracers could reliably differentiate cardiac amyloidosis from other entities that mimic cardiac amyloidosis, such as hypertrophic cardiomyopathy[1]

If cardiac amyloidosis is suspected based on clinical, echocardiographic, or cardiac magnetic resonance (CMR) findings, then[1]:

Analyze blood and urine for evidence of a monoclonal protein **and**

Consider ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP cardiac scintigraphy if ATTR-CM is suspected and AL has been ruled out

*^{99m}Tc-PYP is not FDA approved for the diagnosis of ATTR-CM. Please consult individual labeling for risks.

†A histological diagnosis is needed for patients with evidence of a plasma cell dyscrasia, because the presence of low-grade uptake on a ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP scan is not 100% specific for ATTR-CM, and substantial uptake (Grade 2 or 3) has been reported in more than 20% of patients with AL cardiac amyloidosis. Excluding monoclonal process with serum/urine immunofixation and a serum free light chain (SFLC) assay in all patients with suspected amyloidosis is recommended.[1]

‡Multicenter study conducted to determine the diagnostic value of bone scintigraphy in ATTR-CM patients. Of 1217 evaluable patients, 374 underwent EMB, and 843 were diagnosed with presence and type or absence of amyloid on basis of extracardiac histology combined with echocardiography (echo) with or without CMR.[4]

§Rule out AL: testing for presence of monoclonal protein via serum/urine immunofixation + SFLC assay.[4]

^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP Radionuclide Imaging as a Diagnostic Modality *continued*

KEY RECOMMENDATIONS FOR THE ROLE OF RADIONUCLIDE IMAGING WHEN CARDIAC AMYLOIDOSIS IS SUSPECTED[1]

- The mechanism for the differential uptake in transthyretin amyloid fibril protein (ATTR) vs AL cardiac amyloidosis is unknown, but it has been suggested that the preferential uptake by ATTR may be a result of higher calcium content[1]
- Myocardial imaging with ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP is highly sensitive and specific to diagnose ATTR-CM and may aid in its early detection
- Myocardial uptake of ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP relative to the ribs of Grade ≥2, as determined by semiquantitative visual assessment of planar and SPECT images, is diagnostic of ATTR-CM and removes the need for EMB when AL is ruled out
- Consider cardiac ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP scintigraphy in all patients with unexplained increased left ventricular (LV) wall thickness, heart failure with preserved ejection fraction, familial amyloid polyneuropathy (FAP), family history of amyloidosis, degenerative aortic stenosis with low-flow low gradient in the elderly, and a history of bilateral carpal tunnel syndrome

^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP Radionuclide Imaging
PROS AND CONS[1]

Pros

- Provides critical information on amyloid type
- Offers a definitive diagnosis of ATTR-CM with high sensitivity and specificity in select patients in whom AL has been ruled out*
- Whole-body imaging can occur concurrently, which can identify potential multiorgan involvement
- Nuclear scintigraphy may identify ATTR deposits early in the course of the disease

Cons

- Not 100% specific for patients with evidence of a plasma cell dyscrasia
- It is possible for patients with hereditary ATTR-CM (hATTR-CM) with certain rare mutations in the *TTR* gene to have negative radionuclide imaging findings

*The mechanism for this is unknown.

^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP Radionuclide Imaging as a Diagnostic Modality *continued*

RECOMMENDATIONS FOR INTERPRETATION OF ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP FOR CARDIAC AMYLOIDOSIS[1]

Step 1: Visual interpretation to diagnose ATTR-CM

- Evaluate planar and SPECT images to confirm diffuse radiotracer uptake in the myocardium
- Differentiate myocardial radiotracer uptake from residual blood pool activity, focal myocardial infarct, and overlapping bone (eg, from rib hot spots from fractures) on SPECT images. If excess blood pool activity is noted, recommend repeat SPECT imaging at 3 hours
- If myocardial tracer uptake is visually present on SPECT, proceed to step 2, semiquantitative visual grading. If no myocardial tracer uptake is present on SPECT, the visual grade is 0

Step 2: Semiquantitative visual grading to diagnose ATTR-CM

- Examine planar and SPECT images for relative tracer uptake in the myocardium relative to ribs and grade using the following scale:

Grade 0	No myocardial uptake and normal bone uptake
Grade 1	Myocardial uptake less than rib uptake
Grade 2	Myocardial uptake equal to rib uptake
Grade 3	Myocardial uptake greater than rib uptake with mild/absent rib uptake

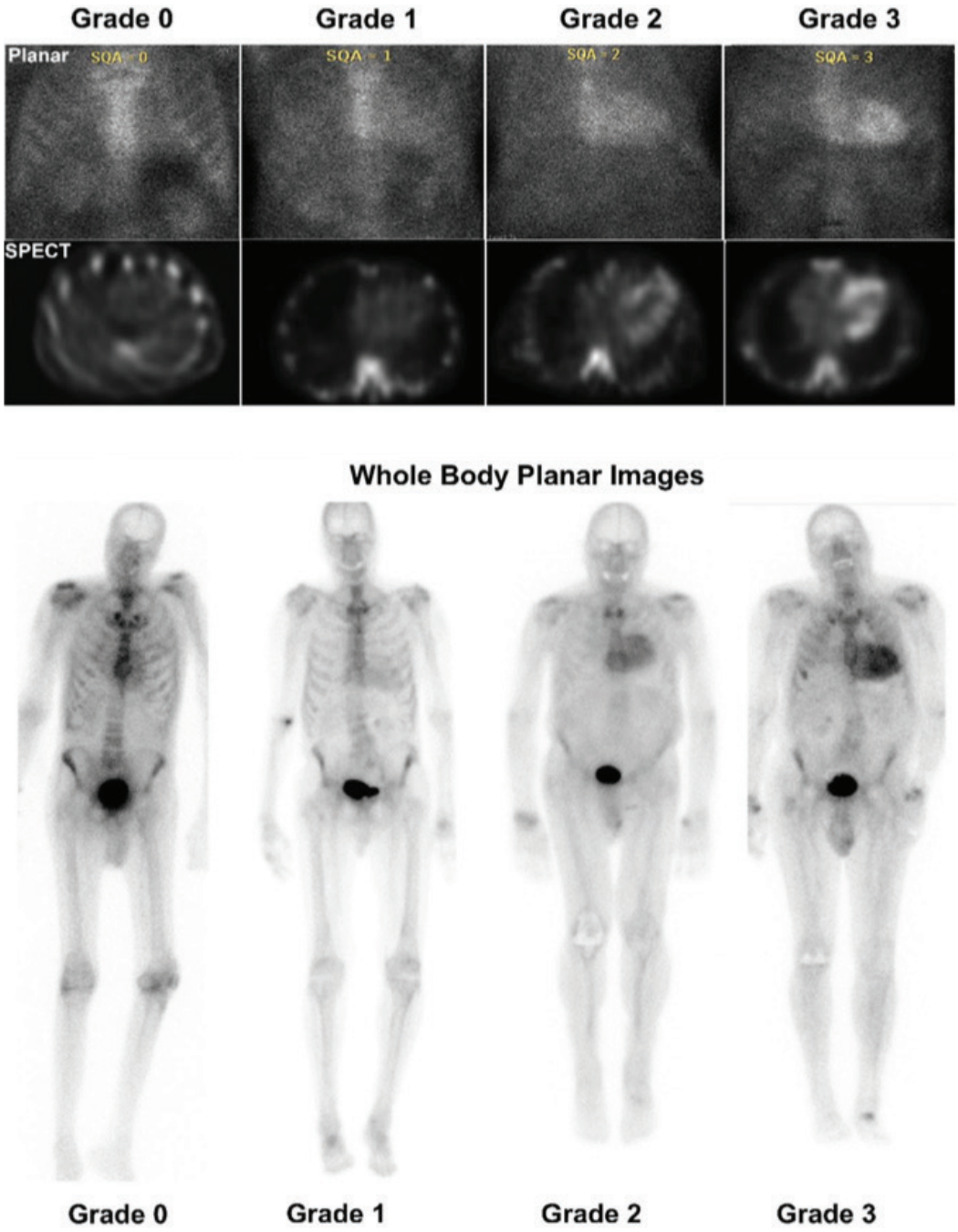
See page 19. Grade 2 or Grade 3 uptake is consistent with ATTR-CM if a monoclonal plasma cell dyscrasia is excluded, as this degree of uptake can be seen in >20% of patients with AL cardiac amyloidosis. Grade 0 and Grade 1 uptake may be observed in AL cardiac amyloidosis and warrants further evaluation to exclude AL amyloidosis. The writing group would like to emphasize the importance of excluding a monoclonal process with serum/urine immunofixation and SFLC assay in all patients with suspected amyloidosis.

Step 3: Heart-to-contralateral lung (H/CL) uptake ratio assessment (when applicable)

- A circular region of interest (ROI) should be drawn over the heart on the anterior planar images with care to avoid sternal overlap and with size adjusted to maximize coverage of the heart without inclusion of adjacent lung. This ROI (same size) should be mirrored over the contralateral chest without inclusion of the right ventricle, to adjust for background and rib uptake (See CARDIAC AMYLOIDOSIS ON RADIONUCLIDE IMAGING on page 21). The heart and contralateral ROIs should be drawn above the diaphragm
- An H/CL ratio is calculated as the fraction of heart ROI mean counts to contralateral lung region of interest (ROI) mean counts
- H/CL ratios of ≥1.5 at 1 hour can accurately identify ATTR-CM if myocardial ^{99m}Tc-PYP uptake is visually confirmed on SPECT and systemic AL amyloidosis is excluded. An H/CL ratio of >1.3 at 3 hours can identify ATTR-CM
- NOTE: Diagnosis of ATTR-CM cannot be made solely based on H/CL ratio alone with ^{99m}Tc-PYP. H/CL ratio is not recommended if there is absence of myocardial uptake on SPECT. Additionally, if the visual grade is 2 or 3, diagnosis is confirmed, and H/CL ratio assessment is not necessary. H/CL ratio is typically concordant with visual grade. If discordant or the visual grade is equivocal, H/CL ratio may be helpful to classify equivocal visual grade of 1 vs 2 as positive or negative

Of note: ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP uptake could be seen in other causes of myocardial injury, including pericarditis, myocardial infarction (regional uptake), and chemotherapy or drug-associated myocardial toxicity.

^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP Radionuclide Imaging as a Diagnostic Modality *continued*



^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP. Anterior planar chest images (top row), SPECT cardiac imaging (middle row), and planar whole-body imaging (bottom row). Cardiac uptake is visually compared with surrounding ribs for a visual grading score as described in the table on page 18. Images with Grade 0, Grade 1, Grade 2, and Grade 3 myocardial uptake of ^{99m}Tc-PYP are shown. (Top panel provided by ASNC Cardiac Amyloidosis Practice Points.)

^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP Radionuclide Imaging as a Diagnostic Modality *continued*

RECOMMENDATIONS FOR STANDARDIZED REPORTING OF ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP IMAGING FOR CARDIAC AMYLOIDOSIS[1]

Parameters	Elements
Demographics	Patient name, age, sex, reason for the test, date of study, prior imaging procedures, biopsy results if available (Required)
Methods	Imaging technique, radiotracer dose and mode of administration, interval between injection and scan, scan technique (planar and SPECT) (Required)
Findings	Image quality Visual scan interpretation (Required) Semiquantitative interpretation in relation to rib uptake (Required) Quantitative findings H/CL ratio (Optional; recommended for positive scans)
Ancillary findings	Whole-body imaging if planar whole-body images are acquired (Optional) Interpret CT for attenuation correction if SPECT/CT scanners are used (Recommended)
Conclusions	1. An overall interpretation of the findings into categories of 1) not suggestive of ATTR-CM; 2) strongly suggestive of ATTR-CM; or 3) equivocal for ATTR-CM after exclusion of a systemic plasma cell dyscrasia. (Required) a. **Not suggestive:** A semiquantitative visual grade of 0. b. **Equivocal:** If diffuse myocardial uptake of ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP is visually confirmed and the semiquantitative visual grade is 1 or there is interpretive uncertainty of Grade 1 vs Grade 2 on visual grading. c. **Strongly suggestive:** If diffuse myocardial uptake of ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP is visually confirmed, a semiquantitative visual grade of 2 or 3. 2. Statement that evaluation for AL amyloidosis by SFLC, serum/urine immunofixation is recommended in all patients undergoing ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP scans for cardiac amyloidosis. (Required) 3. Statement that results should be interpreted in the context of prior evaluation and referral to a hematologist or amyloidosis expert is recommended if either: **a)** Recommended echo/CMR is strongly suggestive of cardiac amyloidosis and ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP is not suggestive or equivocal and/or **b)** FLCs are abnormal or equivocal. (Recommended)

CT, computed tomography.

^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP Radionuclide Imaging as a Diagnostic Modality *continued*

OTHER RADIONUCLIDE IMAGING MODALITIES

Other radionuclide imaging modalities may also play a role in the noninvasive diagnosis of cardiac amyloidosis, including:

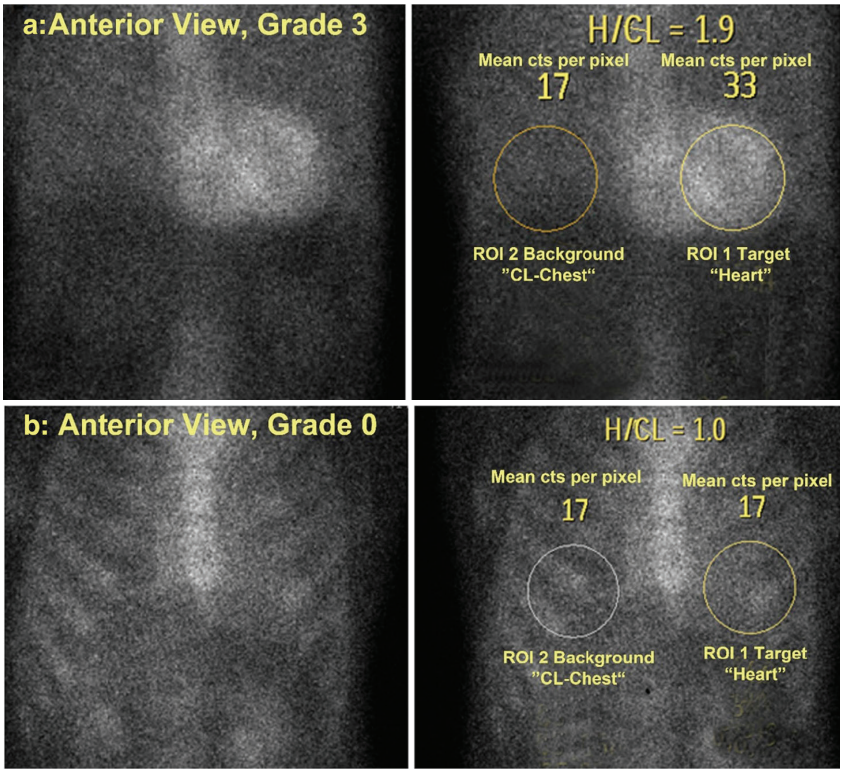
- Targeted amyloid binding ^{18}F-positron emission tomography (PET) tracers, which seem to bind to both ATTR and AL and are highly specific to image amyloid deposits
- Investigational PET tracers include C-Pittsburgh compound B (^{11}C-PIB) and the fluorine-labeled compounds: ^{18}F-florbetapir, ^{18}F-florbetaben, and ^{18}F-flutemetamol
- Another established tracer for imaging myocardial denervation, ^{123}I-meta-iodobenzylguanidine (mIBG), which has been used to image myocardial denervation in familial ATTR-CM

CARDIAC AMYLOIDOSIS ON RADIONUCLIDE IMAGING[1]

Characteristic Appearance

Anterior planar chest views 1 hour after injection of ^{99m}Tc-PYP: a patient with Grade 3 (**a**) and Grade 0 (**b**) ^{99m}Tc-PYP uptake. On the right are the corresponding H/CL ratio methodology with measurement of mean counts per pixel for target (heart) and background (contralateral chest). As shown in this figure, the ROIs should be positioned to minimize overlap with sternal or focal rib uptake and maximize coverage of the heart without including adjacent lung.

Diagnosis of ATTR-CM cannot be made solely based on H/CL ratio alone with ^{99m}Tc-PYP.



Endomyocardial Biopsy (EMB) to Diagnose Cardiac Amyloidosis

EMB is a known diagnostic tool for cardiac amyloidosis. Congo red staining with apple-green birefringence under polarized light is indicative of cardiac amyloidosis.[1,2] Still, EMB comes with limitations and risks, necessitating a multimodality approach using noninvasive imaging techniques, such as echo, CMR, and radionuclide imaging, all of which have evolved as the principal means for cardiac amyloidosis diagnosis and disease management.[1]

EMB
PROS AND CONS[1,2]

Pros

- 100% accuracy in the detection of amyloid deposits

Cons

- Invasive
- Risk for complications
- Requires specialized location and pathologic expertise
- Unable to identify whole-heart amyloid burden, evaluate systemic disease burden, or assess response to therapy

No existing noninvasive diagnostic tools can individually diagnose cardiac amyloidosis AND identify etiologic subtype, necessitating a multimodality cardiac imaging approach to identify this underdiagnosed group of diseases, which may pave the way for future noninvasive diagnostic guidelines for cardiac amyloidosis.[1]

Expert Consensus Recommendations for Diagnosis of Cardiac Amyloidosis[2]

Criteria for Diagnosis	Subtype
Histological Diagnosis of Cardiac Amyloidosis: EMB*	
1. EMB positive for cardiac amyloidosis with Congo red staining with apple-green birefringence under polarized light; typing by immunohistochemistry and/or mass spectrometry at specialized centers	AL, ATTR, other subtypes
Histological Diagnosis of Cardiac Amyloidosis: Extracardiac Biopsy	
1. ATTR-CM is diagnosed when below criteria are met: a. Extracardiac biopsy proven ATTR amyloidosis **AND** b. Typical cardiac imaging features (as defined below)	ATTR
2. AL cardiac amyloidosis is diagnosed when below criteria are met: a. Extracardiac biopsy proven AL amyloidosis relative to ribs as determined by semiquantitative visual assessment of planar and SPECT images **AND** b. Typical cardiac imaging features (as defined below) **OR** c. Abnormal cardiac biomarkers: abnormal age-adjusted NT-proBNP or abnormal Troponin T/I/Hs-Troponin with all other causes for these changes excluded	AL
Clinical Diagnosis of ATTR-CM: ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP	
3. ATTR-CM is diagnosed when below criteria are met: a. ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP Grade 2 or 3 myocardial uptake of radiotracer relative to ribs as determined by semiquantitative visual assessment of planar and SPECT images **AND** b. Absence of a clonal plasma cell process as assessed by SFLC and serum and urine immunofixation **AND** c. Typical cardiac imaging features (as defined below)	ATTR
Typical Imaging Features of Cardiac Amyloidosis	
Typical cardiac echo or CMR or PET features: ANY of the below imaging features with all other causes for these cardiac manifestations, including hypertension, reasonably excluded	
1. Echo a. LV wall thickness >12 mm b. Relative apical sparing of global LS ratio (average of apical LS/average of combined mid+basal LS >1) c. ≥ Grade 2 diastolic dysfunction†	ATTR/AL
2. CMR a. LV wall thickness >ULN for sex on SSFP cine CMR b. Global ECV >0.40 c. Diffuse LGE† d. Abnormal gadolinium kinetics typical for amyloidosis, myocardial nulling prior to blood pool nulling	ATTR/AL
3. PET: ^{18}F-florbetapir† or ^{18}F-florbetaben PET†‡ a. Target to background (LV myocardium to blood pool) ratio >1.5 b. Retention index >0.030 min^{-1}	ATTR/AL

These consensus recommendations were based on moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, registries, or meta-analyses of such studies. The PET recommendations were based on more limited data.

*EMB should be considered in cases of equivocal ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP scan. When ^{99m}Tc-PYP/^{99m}Tc-DPD/^{99m}Tc-HMDP is positive in the context of any abnormal evaluation for serum/urine immunofixation or SFLC assay, or MGUS, this should not be seen as diagnostic for ATTR-CM. In these instances, referral to a specialist amyloid center for further evaluation and consideration of biopsy is recommended.

†Off-label use of FDA-approved commercial products.

‡^{18}F-flutemetamol not studied systematically in the heart. ^{11}C-Pittsburgh B compound is not FDA approved and not available to sites without a cyclotron in proximity.

^{99m}Tc-DPD, ^{99m}technetium-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc-HMDP, ^{99m}technetium-labeled hydroxymethylene diphosphonate; ^{99m}Tc-PYP, ^{99m}technetium-labeled pyrophosphate; AL, immunoglobulin light chain amyloid fibril protein; ATTR, transthyretin amyloid fibril protein; CMR, cardiac magnetic resonance; ECV, extracellular volume; EMB, endomyocardial biopsy; LGE, late gadolinium enhancement; LS, longitudinal strain; LV, left ventricular; MGUS, monoclonal gammopathy of uncertain significance; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PET, positron emission tomography; SFLC, serum free light chain; SPECT, single-photon emission computed tomography; SSFP, steady-state free precession; ULN, upper limit of normal.

References: 1. Dorbala S, Ando Y, Bokhari S, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: part 1 of 2—evidence base and standardized methods of imaging. *J Nucl Cardiol.* 2019;26(6):2065-2123. doi:10.1007/s12350-019-01760-6. Addendum: *J Nucl Cardiol.* Published online July 1, 2021. doi:10.1007/s12350-020-02455-z **2.** Dorbala S, Ando Y, Bokhari S, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: part 2 of 2—diagnostic criteria and appropriate utilization. *J Nucl Cardiol.* 2020;27(2):659-673. doi:10.1007/s12350-019-01761-5 **3.** Laboratory of Cardiac Energetics. National Heart, Lung, and Blood Institute Division of Intramural Research website. What are the technological advantages and limitations (disadvantages) of MRI? https://dir.nhlbi.nih.gov/labs/lce/cmri/mri-advantages-limitation.asp. Accessed November 14, 2019. **4.** Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation.* 2016;133(24):2404-2412.

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Adapted from Dorbala Part 2.

These consensus recommendations were based on moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, registries, or meta-analyses of such studies. The PET recommendations were based on more limited data.

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