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

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ABSTRACT

Cardiac amyloidosis is emerging as an underdiagnosed cause of heart failure and mortality. Growing literature suggests that a noninvasive diagnosis of cardiac amyloidosis is now feasible. However, the diagnostic criteria and utilization of imaging in cardiac amyloidosis are not standardized. In this paper, Part 2 of a series, a panel of international experts from multiple societies define the diagnostic criteria for cardiac amyloidosis and appropriate utilization of echocardiography, cardiovascular magnetic resonance imaging, and radionuclide imaging in the evaluation of patients with known or suspected cardiac amyloidosis. (*J Cardiac Fail 2019;25:854−865*)
Key Words: Cardiac amyloidosis, diagnosis, appropriate use, expert consensus, multimodality.

Introduction

Cardiac amyloidosis is increasingly recognized as an important cause of heart failure with preserved ejection fraction (EF)[1] and carries a high morbidity and mortality.[2,3] Emerging imaging methods have facilitated earlier diagnosis[4−6] and improved prognostication[7,8] and management. The diagnostic criteria for cardiac amyloidosis, however, need to be updated to include these novel imaging tools.

A multi-societal writing group with expertise in cardiovascular imaging and cardiac amyloidosis has been assembled by the American Society of Nuclear Cardiology (ASNC) with representatives from the American College of Cardiology (ACC), the American Heart Association (AHA), the

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American Society of Echocardiography (ASE), the European Association of Nuclear Medicine (EANM), the Heart Failure Society of America (HFSA), the International Society of Amyloidosis (ISA), the Society of Cardiovascular Magnetic Resonance imaging (SCMR), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI). This writing group has established consensus recommendations on imaging cardiac amyloidosis from this panel of multidisciplinary experts. Part 1 documents the evidence base for multimodality imaging in cardiac amyloidosis and defines standardized imaging protocols. Part 2 has the following aims:

1) Develop consensus diagnostic criteria for cardiac amyloidosis incorporating advanced echocardiography, cardiovascular magnetic resonance (CMR), and radionuclide imaging.
2) Identify consensus clinical indications for noninvasive imaging in cardiac amyloidosis to guide patient management through a rigorous application of the modified Delphi method.
3) Address the appropriate utilization of echocardiography, CMR, and radionuclide imaging in these clinical scenarios.

Diagnostic Criteria, Clinical Indications, and Appropriate Utilization

Expert consensus criteria were developed based on histologic, clinical, and imaging features with accompanying certainty of recommendation. The appropriate utilization of multiple imaging modalities was assessed using clinical scenarios that represent diverse patient presentations and address the diagnostic and prognostic capabilities of noninvasive imaging. The goal of this document is to determine which modalities may be reasonable for a specific indication rather than to identify one test that is best.

Methods

In order to accomplish this goal, a rating panel of clinical experts in cardiac amyloidosis was assembled. As recommended by the RAND-UCLA Appropriateness Manual, this group included representatives from relevant clinical societies, all of whom have extensive expertise in the management of cardiac amyloidosis.[9] The group was recruited internationally from diverse geographical locations. All group representatives practice in academic settings, which is typical given the clinical complexity of this disorder. Experts with extensive imaging expertise were expressly excluded from this panel to prevent bias in the scoring process, as experts with expertise in a single imaging modality might tend to rate their favored imaging modality as more appropriate than the remainder. The final ratings panel included 7 clinical experts.[9] This group developed expert consensus recommendations on criteria for the diagnosis of cardiac amyloidosis via histologic, imaging, and cardiac biomarkers. The rating panel then engaged in an exercise using the modified Delphi technique for a robust evaluation of appropriateness.[10]

Indication Development

A standardized approach was used to ensure inclusion of the majority of clinical scenarios encountered in the evaluation and management of cardiac amyloidosis. Despite best efforts, however, the writing group acknowledges that clinical presentations vary, and not every relevant clinical scenario is represented. These scenarios were organized into several broad categories representing key areas of cardiac amyloidosis clinical care:

- Assessment for cardiac involvement in asymptomatic individuals;
- Screening for cardiac amyloidosis in patients with symptomatic heart failure;
- Evaluation of biopsy-proven light-chain (AL) and amyloidogenic transthyretin (ATTR) cardiac amyloidosis;
- Follow-up testing for new or worsening cardiac symptoms;
- Other diverse clinical scenarios/conditions; and
- Prior testing suggestive of cardiac amyloidosis.

Once a final list was developed, the larger writing group, comprised of imaging experts in the various disciplines, provided feedback prior to the final indication determination.

Rating Process

Once the indications were finalized, the rating panel scored them independently. For each indication, the rating panel was asked to rate its appropriateness in the evaluation and management of cardiac amyloidosis. The following definition of appropriate use was adapted from prior appropriate use documents [11–13]: *An appropriate imaging study is one in which the expected incremental information, combined with clinical judgement, exceeds the expected negative consequences by a sufficiently wide margin for a specific indication that the procedure is generally considered acceptable care and a reasonable approach for the indication.*[14]

The rating group used a scale from 1 to 9. These scores were divided into 3 general categories: Appropriate (A), May Be Appropriate (M), or Rarely Appropriate (R) in accordance with published appropriate use criteria methodology and prior appropriate use documents.[12,15–17]

Appropriate (Score 7–9)

An indication scored from 7 to 9 represents an appropriate option for management of patients in this population due to benefits generally outweighing risks; it should be viewed as an effective option for individual care plans, although the imaging procedure may not always be necessary depending on physician judgement and patient-specific preferences (ie, the procedure is generally acceptable and is generally reasonable for the indication).

May Be Appropriate (Score 4–6)

An indication scored from 4 to 6 is considered at times an appropriate option for management of patients in this

population due to variable evidence or agreement regarding the risk-benefit ratio, potential benefit based on practice experience in the absence of evidence, and/or variability in the population; the effectiveness of this indication for individual care must be determined by a patient's physician in consultation with the patient based on additional clinical variables and judgement along with patient preferences (ie, the procedure may be acceptable and may be reasonable for the indication). A categorization of May Be Appropriate may also imply that further research and/or patient information is needed to classify the indication definitively.

Rarely Appropriate (Score 1–3)

An indication scored from 1 to 3 is rarely an appropriate option for management of patients in this population for this clinical indication due to a lack of a clear benefit/risk advantage; it is rarely an effective option for individual care plans; exceptions should have documentation of the clinical reasons for proceeding with this care option (ie, procedure is not generally acceptable and is not generally reasonable for the indication).

The division of the scores into these 3 broad categories is somewhat arbitrary, and the raters were instructed to consider the numeric range as a continuum. Recognizing that there is variability in many patient factors, local practice patterns, and a lack of data on use of imaging across clinical scenarios and indications, the rating panel members were asked to independently rate the appropriateness of using each imaging modality for the general category and the specific clinical indication based on the best available evidence, including guidelines and key references wherever possible.[10]

After rating the indications independently, the total results were tabulated, and each rater was provided with their individual scores and de-identified scores from all other panel members. The panel was convened for conference calls for discussion of each indication. The clinical indications were modified if needed based on the discussion. This meeting was facilitated by non-rating representatives of the writing panel who served as unbiased moderators and facilitated group dynamics to optimize the process. The moderators were free of significant relationships with industry and were unbiased relative to the topics under consideration. Following the meeting, panel members were asked to independently provide their scores for each clinical indication in a second round of ratings, taking into consideration the discussion from the call. For indications with continued significant dispersion of scores, a second conference call and third round of ratings occurred.

Median scores were calculated. A median panel score of 7 to 9 without disagreement was considered "Appropriate". A median panel score of 1 to 3 without disagreement was considered "Rarely Appropriate". A median panel score of 4 to 6 or any median with disagreement was classified as "May Be Appropriate". Agreement was classified as having no more than 2 panelists provide ratings in an alternate category (this corresponded to >70% consensus).[9,16]

Assumptions

The following list of assumptions to be followed was adapted from methodology recommendations and prior appropriate use documents and was communicated to the expert rating panel members prior to their rating of the indications.[12,15,17,18]

1) All imaging studies are assumed to be locally available and to be performed in accredited imaging laboratories in accordance with published criteria for quality cardiac diagnostic testing using state-of-the-art, certified imaging equipment.
2) All imaging is assumed to be performed according to the standard of care as defined by the peer-reviewed medical literature.
3) All interpreting physicians are qualified and certified to supervise the imaging procedure and appropriately report the findings.
4) In clinical scenarios, the clinical status listed is assumed to be valid as stated (asymptomatic patients are truly asymptomatic) and no extenuating circumstances are to be taken into consideration (patient willingness to receive treatment, clinical stability) unless specifically noted.
5) Appropriateness should be rated independently of the appropriateness of any prior diagnostic imaging that may have been performed.
6) All patients are assumed to be receiving optimal therapy conforming to current standards of care, including contemporary heart failure therapy and cardiovascular risk-factor modification, unless specifically noted.
7) Imaging indicated for surveillance to assess disease progression or response to therapy is assumed to be performed solely because the indicated time period elapsed rather than due to any change in clinical circumstances.
8) Radiation risk was not considered. Although theoretical concerns have been raised that diagnostic imaging-related ionizing radiation may result eventually in an increased risk of cancer in the exposed population, this has not been proven. Moreover, in this population with high risk for heart failure and neuropathy, the benefit of a small dose of radiation was felt to outweigh the risk, especially when compared with a strategy with invasive endomyocardial biopsy. This risk can be minimized by preventing inappropriate use and by optimizing studies with the lowest radiation dose possible.[19]
9) Cost of the imaging procedures is not to be considered in accordance with recommended appropriateness scoring methods.[9] Cost is recognized to be an important issue from a policy perspective, but expert physician appropriateness rating has been shown to agree with cost-effectiveness models.[20,21]

Definitions

1) No cardiac symptoms
The absence of the following symptoms was used to indicate that no cardiac symptoms are present. These include chest pain, fatigue, effort intolerance, shortness of breath, palpitations, dizziness/lightheadedness, syncope, orthopnea, paroxysmal nocturnal dyspnea, bloating, leg swelling, leg or jaw claudication.

2) *TTR* gene carrier
A *TTR* gene carrier refers to individuals who harbor one of the more than 120 mutations in the transthyretin gene that have been associated with the development of transthyretin amyloidosis.[22]

3) Recurrent testing
Recurrent testing refers to performance of the same imaging modality more than once, excluding non-diagnostic studies, to identify cardiac involvement in the setting of prior negative testing; the interval between studies is not addressed.

4) Biopsy-proven AL cardiac amyloidosis
The diagnosis of AL amyloidosis requires a positive tissue biopsy showing amyloid deposits in the presence of clinical, imaging, or laboratory signs of organ involvement. The amyloid deposits should exhibit a characteristic affinity for Congo red staining with birefringence under polarized light. Typing of AL amyloidosis is confirmed on immunohistochemistry and/or mass spectroscopy. Electron microscopy of amyloid deposits is rarely performed but reveals prototypic rigid, nonbranching 10- to 12-nm-width fibrils. Amyloid deposits can be detected at accessible sites, such as abdominal fat, bone marrow, or minor salivary glands, and the biopsy of the involved organ is not always necessary.[23]

5) Abnormal NT-proBNP and Troponin T
Cardiac biomarkers (N-terminal pro-brain natriuretic peptide, [NT-proBNP] and troponins) are used for staging with different cutoffs.[24–26] In AL amyloidosis, NT-proBNP has >99% diagnostic sensitivity, with all patients with heart involvement having an elevated (≥332 ng/L) NT-proBNP.[27]

6) Monoclonal gammopathy of uncertain significance (MGUS)
A premalignant, clonal plasma cell disorder characterized by the presence of a usually small monoclonal (M) protein and <10% clonal plasma cell clones in the bone marrow in the absence of multiple myeloma or related lymphoplasmacytic malignancies.[28,29]

7) Abnormal free light chains
Abnormal free light chains (FLCs) are defined by an abnormal serum kappa and lambda immunoglobulin FLC ratio. The reference interval of FLC ratio may vary by the assay method used or in the setting of renal failure. The reference range of the FLC ratio as measured by binding site is between 0.26 and 1.65 in patients with normal renal function or between 0.31 and 3.7 in patients with renal failure. The reference range of the FLC ratio as measured by Siemens is between 0.31 and 1.56.

8) Symptomatic heart failure
Symptomatic heart failure refers to patients who have New York Heart Association (NYHA) Class II or greater symptoms adapted from Dolgin et al[30] from original source.[31]

9) Unexplained heart failure
Unexplained heart failure refers to heart failure without a known etiology, in particular, ischemic heart disease or valvular heart disease.

10) Increased wall thickness
Echo mean left ventricular (LV) wall thickness of >12 mm with no other known cardiac cause.[23]

11) Preserved LV ejection fraction
Heart failure with preserved ejection fraction is defined per ACC/AHA heart failure guidelines as an LV ejection fraction of ≥40%.[32]

12) Low-flow aortic stenosis
A low-flow aortic stenosis was defined as low transvalvular mean aortic gradient (≤40 mmHg) or stroke volume index of <35 mL/m^2 in the context of reduced LV ejection fraction (classical low flow) or preserved LV ejection fraction (paradoxical low flow).[33]

13) Unexplained peripheral sensorimotor neuropathy
Patient-reported paresthesias typical for this type of neuropathy in which no known cause has been identified (eg, diabetes, alcohol abuse, or toxicity).

14) Known or suspected familial amyloidosis
Documented amyloidosis in one or more closely related family members, such as a parent, brother or sister, uncle or aunt, and particularly so if a mutation of an amyloidogenic protein has been identified. In addition, an unexplained clinical picture of peripheral polyneuropathy and/or cardiomyopathy in several family members in a number of generations.

15) Biopsy-proven ATTR cardiac amyloidosis
Endomyocardial biopsy showing amyloid deposits, which are confirmed on immunohistochemistry and/or mass spectroscopy to be transthyretin.

16) Contraindication to CMR
As the CMR scanner generates a very powerful static magnetic field, certain implanted cardiac devices and ferromagnetic prostheses may pose a safety concern from movement, arrhythmia induction, or tissue heating

from the magnetic fields. Each device must be evaluated on an individual basis for safety before proceeding with CMR. Because of a potential risk of nephrogenic systemic fibrosis, gadolinium use is contraindicated in individuals with estimated glomerular filtration rate <30 mL/min/1.73 m^2.[34]

17) Unexplained bilateral carpal tunnel syndrome
Carpal tunnel syndrome is defined as a symptomatic compression neuropathy of the median nerve at the level of the wrist, characterized physiologically by evidence of increased pressure within the carpal tunnel and decreased function of the nerve at that level.[35] Bilateral carpal tunnel syndrome in the absence of rheumatoid arthritis or known trauma is defined as unexplained.

18) Unexplained biceps tendon rupture
Biceps tendon rupture in the absence of trauma, such as severe heavy lifting.

19) Echo, CMR, or ^{99m}Tc-PYP/DPD/HMDP imaging study suggestive of cardiac amyloidosis
An echocardiogram (Echol), CMR, or ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP)/^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD)/^{99m}Tc-hydroxymethylenediphosphonate (^{99m}Tc-HMDP) radionuclide imaging study with findings of cardiac amyloidosis as specified in Table 1, Expert Consensus Recommendations for Diagnosis of Cardiac Amyloidosis.

Diagnostic Criteria for Cardiac Amyloidosis

The current diagnosis of cardiac amyloidosis is not standardized. A multicenter consensus paper has proposed a diagnostic algorithm for the evaluation of ATTR cardiac amyloidosis incorporating echocardiography, CMR, and bone-avid radiotracers[36]; however, no formal diagnostic criteria have been reported. An international consensus document on AL amyloidosis defines cardiac involvement by either endomyocardial biopsy or by systemic biopsy demonstrating AL amyloid and elevated LV wall thickness on echocardiography without alternative cardiac cause.[23] However, advances in noninvasive imaging and cardiac biomarkers in cardiac amyloidosis during the past 2 decades have led to improved methods of assessment beyond echocardiographic wall thickness. These tools have extensive validation in the literature, as described above, but were not included in the consensus document. They allow for more sensitive and earlier detection of disease. Therefore, there is a need for updated diagnostic criteria that incorporate these novel methods. Expert consensus recommendations for criteria for diagnosis of cardiac amyloidosis are provided in Table 1 with accompanying certainty of recommendation. Cardiac amyloidosis is confirmed with a positive endomyocardial biopsy for amyloid fibrils. In the absence of endomyocardial biopsy-proven disease, cardiac amyloidosis can be diagnosed using a combination of extracardiac biopsy, ^{99m}Tc-PYP/DPD/HMDP scintigraphy, myocardial uptake of targeted positron emission tomography (PET) amyloid tracers, and echocardiographic and CMR findings as shown in Table 1. In the absence of a clonal plasma cell process, ^{99m}Tc-PYP/DPD/HMDP scintigraphy consistent with ATTR cardiac amyloidosis combined with consistent echo or CMR findings obviates the need for invasive endomyocardial or extracardiac biopsy.

Appropriate Utilization of Multimodality Imaging in Cardiac Amyloidosis

The appropriate utilization ratings for echocardiography, CMR, and radionuclide scintigraphy (^{99m}Tc-PYP/DPD/HMDP) for the 32 clinical indications are provided in Table 2. There were 30 evaluable indications for echocardiography, of which 27 were rated as "Appropriate" and 3 "May Be Appropriate". Cardiac magnetic resonance likewise had 30 evaluable indications, of which 19 were rated as "Appropriate", 9 as "May Be Appropriate", and 2 as "Rarely Appropriate". ^{99m}Tc-PYP/DPD/HMDP scintigraphy had 31 evaluable indications, of which 10 were "Appropriate", 6 were "May Be Appropriate", and 15 "Rarely Appropriate". Echocardiography was rated as "Appropriate" for all assessed clinical indications except for some more frequent intervals of assessment of cardiac response to therapy or disease progression, which were rated as "May Be Appropriate". Except for new onset symptomatic heart failure, CMR had more mixed ratings. ^{99m}Tc-PYP/DPD/HMDP scintigraphy was rated as "Appropriate" or "May Be Appropriate" for all indications other than those involving suspected light-chain amyloidosis or biopsy-proven AL or ATTR cardiac amyloidosis, which were classified as "Rarely Appropriate".

Although cost considerations, radiation risk, and availability of technology were not considered during the rating process, the rating panel did want to emphasize that these issues may influence the choice of imaging modality, particularly with regard to the frequency of repeat testing. The panel also wanted to stress the importance of consideration of referral to specialized amyloidosis centers, particularly in familial amyloidosis, AL cardiac amyloidosis, or for consideration of novel therapies (Table 3).

Clinical Scenario #1: Identifying Cardiac Involvement: No Cardiac Symptoms

For asymptomatic gene carriers, echocardiography and radionuclide scintigraphy (^{99m}Tc-PYP/DPD/HMDP) were rated as "Appropriate", whereas CMR was rated "May Be Appropriate". Because the age of onset and phenotypic manifestation of disease vary by the type of mutation, imaging was determined by the panel to be appropriate in some situations but not for others, resulting in a rating of "May Be Appropriate". In particular, the panel discussed that extracel-

Table 1. Expert Consensus Recommendations for Diagnosis of Cardiac Amyloidosis

Criteria for Diagnosis	Subtype
Histological Diagnosis of Cardiac Amyloidosis: Endomyocardial Biopsy*	
1. Endomyocardial biopsy 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 cardiac amyloidosis 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 **AND** b. Typical cardiac imaging features (as defined below) **OR** c. Abnormal cardiac biomarkers: abnormal age-adjusted NT-pro BNP or abnormal Troponin T/I/Hs-Troponin with all other causes for these changes excluded	AL
Clinical Diagnosis of ATTR Cardiac Amyloidosis: ^{99m}Tc-PYP, DPD, HMDP	
3. ATTR cardiac amyloidosis is diagnosed when below criteria are met: a. ^{99m}Tc-PYP, DPD, HMDP Grade 2 or 3 myocardial uptake of radiotracer **AND** b. Absence of a clonal plasma cell process as assessed by serum FLCs 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

LGE, late gadolinium enhancement; LS, longitudinal strain; SSFP, steady-state free precession; ULN, upper limit of normal, per Kawel et al[39] at mid-cavity level ULN for women/men were 7/9mm (long axis) and 7/8mm (short axis), respectively.

These consensus recommendations were based on moderate-quality evidence from one 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.

* Endomyocardial biopsy should be considered in cases of equivocal ^{99m}Tc-PYP, DPD, HMDP scan. When ^{99m}Tc-PYP, DPD, HMDP is positive in the context of any abnormal evaluation for serum/urine immunofixation or serum free light-chain assay, or MGUS, this should not be seen as diagnostic for ATTR cardiac amyloidosis. 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.

lular volume assessment by CMR has the potential to identify disease earlier in asymptomatic gene carriers compared with echocardiography. For asymptomatic patients with elevated cardiac biomarkers and either biopsy-proven systemic AL amyloidosis or MGUS with abnormal FLC levels, echocardiography and CMR were rated as "Appropriate", but ^{99m}Tc-PYP/DPD/HMDP scintigraphy was "Rarely Appropriate". The panel discussed that the magnitude of biomarker abnormality should play a role in determining the use of imaging. In particular, because of the high prevalence of MGUS, as well as ATTR wild-type (ATTRwt) in older individuals, use of imaging may be guided by serum biomarker levels, particularly in AL amyloidosis patients, in whom NT-proBNP is a sensitive marker of cardiac involvement.

Clinical Scenario #2: Screening for Cardiac Amyloidosis: New Symptomatic Heart Failure

In the 9 clinical indications encompassing patients with new symptomatic heart failure considered in this document, echocardiography and CMR were rated as uniformly "Appropriate" for screening for cardiac amyloidosis. This is consistent with the appropriate rating given to CMR and echocardiography for evaluation of newly suspected heart failure in the most recent appropriate utilization report addressing heart failure.[18] ^{99m}Tc-PYP/DPD/HMDP scintigraphy was also "Appropriate" for all of these indications except the 2 addressing patients in whom AL cardiac amyloidosis is suspected due to elevated FLC levels or monoclonal gammopathy, in whom bone scintigraphy alone is insufficient to establish the type of cardiac amyloidosis

and for whom a biopsy is required. ^{99m}Tc-PYP/DPD/HMDP scintigraphy may occasionally be considered prior to endomyocardial biopsy in instances where ATTR cardiac amyloidosis is in the differential diagnosis. The panel discussed that individuals with unexplained peripheral sensorimotor neuropathy should have diabetes mellitus and other causes of neuropathy excluded as a cause and may benefit from FLC level testing or genetic sequencing of amyloidogenic proteins to guide need for imaging.

Clinical Scenarios #3 and #4: Evaluation of Biopsy-Proven AL and ATTR Cardiac Amyloidosis

Although biopsy-proven AL and ATTR cardiac amyloidosis qualifies as a definitive diagnosis, imaging was still considered to assess amyloid burden, response to therapy, or eligibility for stem cell transplant. For these indications, ^{99m}Tc-PYP/DPD/HMDP scintigraphy is not performed clinically and was rated as "Rarely Appropriate". For quantifying

Table 2. Appropriate Utilization Rating of Multimodality Imaging for the Assessment of Cardiac Amyloidosis

Clinical scenarios	Echo -AUC Category (median score)	CMR -AUC Category (median score)	^{99m}Tc-PYP/DPD/HMDP -AUC Category (median score)
1. Identifying cardiac involvement: No cardiac symptoms			
1.1 Asymptomatic *TTR* gene carrier, initial evaluation	A (7)	M (6)	A (8)
1.2 Asymptomatic *TTR* gene carrier, recurrent testing	A (7)	M (6)	A (7.5)
1.3 Biopsy-proven systemic AL amyloidosis: NT-proBNP age-adjusted abnormal or troponin abnormal	A (9)	A (7)	R (1)
1.4 MGUS with abnormal FLC levels: NT-proBNP age-adjusted abnormal or troponin abnormal	A (8)	A (7)	R (2)
2. Screening for cardiac amyloidosis: New symptomatic heart failure			
2.1 Individuals of any age with elevated FLC levels	A (9)	A (8)	R (2.5)
2.2 African-Americans age >60 years with unexplained heart failure	A (9)	A (8)	A (8)
2.3 African-Americans age >60 years with unexplained increased LV wall thickness	A (9)	A (8)	A (9)
2.4 Non-African-Americans age >60 years with unexplained heart failure and increased LV wall thickness	A (9)	A (8)	A (8)
2.5 Individuals >60 years with low-flow low-gradient aortic stenosis**	NA	A (8)	A (7)
2.6 Individuals with heart failure and unexplained peripheral sensorimotor neuropathy	A (8)	A (8)	A (8)
2.7 Individuals with known or suspected familial amyloidosis	A (8)	A (8)	A (8)
2.8 Individuals with monoclonal gammopathy, including multiple myeloma	A (8)	A (8)	R (2)
3. Evaluation of biopsy-proven AL cardiac amyloidosis			
3.1 Quantify cardiac amyloid burden	A (7)	A (9)	R (1)
3.2 Assess cardiac response to therapy/disease progression in AL cardiac amyloidosis every 6 months*	M (5) †	R (3)	R (1)
3.3 Assess cardiac response to therapy/disease progression in AL cardiac amyloidosis every 12 months*	M (5)	M (6)	R (1)

(*continued*)

3.4 Assess cardiac response to therapy/disease progression in AL cardiac amyloidosis every 24 months*	A (7)	A (8)	R (1)
3.5 Guide eligibility for stem cell transplant in systemic AL amyloidosis	A (8)	M (5)	R (1)
4. Evaluation of biopsy-proven ATTR cardiac amyloidosis			
4.1 Quantify amyloid burden	A (8)	A (9)	R (2)
4.2 Assess cardiac response to therapy/disease progression in ATTR cardiac amyloidosis every 6 months*	M (4) †	R (2)	R (2)
4.3 Assess cardiac response to therapy/disease progression in ATTR cardiac amyloidosis every 12 months*	A (7)	M (5)	R (2.5)
4.4 Assess cardiac response to therapy/disease progression in ATTR cardiac amyloidosis every 24 months*	A (8)	A (8)	R (3)
4.5 Contraindication to CMR (intracardiac devices or renal insufficiency)	A (8)	NA	R (3)
5. Follow-up testing: New or worsening cardiac symptoms			
5.1 *TTR* gene carrier	A (8)	A (7)	A (8)
5.2 AL amyloidosis	A (8)	A (7)	R (1)
5.3 ATTR amyloidosis	A (8)	A (7)	A (7.5)
6. Other clinical conditions associated with amyloidosis			
6.1 Individuals >60 years with unexplained bilateral carpal tunnel syndrome	A (7)	M (5) †	M (6.5) †
6.2 Individuals with unexplained bilateral carpal tunnel syndrome and elevated FLC levels	A (7)	M (5)	M (5.5)
6.3 Individuals >60 years with heart failure and unexplained biceps tendon rupture	A (7)	M (5)	M (6)
6.4 Adults, especially elderly men, with unexplained neuropathy, other arrhythmias in the absence of usual risk factors and no signs/symptoms of heart failure	A (7)	M (5)	M (6)

NA, not assessed.
*Time interval may vary based on the clinical status of the patient and local clinical practice.
**Although most patients with cardiac amyloidosis will have preserved LV ejection fraction or "paradoxical" low-flow, low-gradient AS, LV ejection fraction may be reduced or mid-range in some cases.
†Indicates lack of consensus for rating among experts.

cardiac amyloid burden, echocardiography and CMR were rated as "Appropriate". With regard to assessing cardiac response to therapy and disease progression in AL and ATTR cardiac amyloidosis, the raters agreed that assessment every 24 months was "Appropriate". More frequent evaluation varied across expert amyloidosis centers.

Clinical Scenario #5: Follow-Up Testing: New or Worsening Cardiac Symptoms

In *TTR* gene carriers or patients with AL or ATTR amyloidosis who have new or worsening cardiac symptoms, the panel rated echocardiography, CMR, and ^{99m}Tc-PYP/DPD/

Table 3. Disclosures

Authors	Advisory Board	Research Grant	Consulting Fee	Honoraria	Stock Ownership
Jamieson M. Bourque, MD		Astellas	Pfizer		Locus Health
Angela Dispenzieri, MD		Celgene, Takeda, Janssen, Pfizer, Alnylam Pharmaceuticals, Prothena Bioscience			
Sharmila Dorbala, MD, MPH	GE Healthcare, Pfizer		GE Healthcare, Proclara Biosciences, Advanced Accelerator Applications	Pfizer	
Rodney H. Falk, MD			Alnylam, Ionis, Akcea Therapeutics, Eidos Therapeutics		
Julian D. Gillmore, MD, PhD	Alnylam, GlaxoSmithKline				
Raymond Y. Kwong, MD, MPH		Siemens Medical Systems, Bayer, GlaxoSmithKline, Alynlam, Myokardia, the SCMR			
Mathew S. Maurer, MD	Prothena Biosciences, GlaxoSmithKline, Ionis	Pfizer, Alnylam			
Giampaolo Merlini, MD	Prothena Biosciences, Pfizer, Ionis Pharmaceuticals				
Edward J. Miller, MD, PhD		Bracco Diagnostics	GE Healthcare, Pfizer		
Venkatesh L. Murthy, MD, PhD		INVIA Medical Imaging Solutions		Ionetix, Bracco Diagnostics	General Electric
Claudio Rapezzi, MD	Alnylam, Prothena Biosciences, GlaxoSmithKline	Pfizer			
Frederick L. Ruberg, MD			Caelum Biosciences, Alynlam, Prothena Biosciences		
Sanjiv J. Shah, MD		Actelion, AstraZeneca, Corvia Medical	Actelion, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Cardiora, Eisai, Gilead Sciences, Ironwood Pharmaceuticals, Merck, MyoKardia, Novartis, Sanofi, United Therapeutics Corp.	Pfizer	

HMDP scintigraphy as "Appropriate". ^{99m}Tc-PYP/DPD/HMDP scintigraphy was rated as "Rarely Appropriate" for patients with AL amyloidosis. Notably, ATTR cardiac amyloidosis has been reported in long-term survivors of AL amyloidosis, and ^{99m}Tc-PYP/DPD/HMDP scintigraphy may have a potential role in those rare instances.[37]

Clinical Scenario #6: Other Indications and Prior Testing

The rating panel evaluated several clinical indications emerging as high risk for potential cardiac amyloidosis and rated echocardiography as "Appropriate" and CMR and ^{99m}Tc-PYP/DPD/HMDP scintigraphy as "May Be Appropriate". The evolving literature suggesting possible ATTR cardiac amyloidosis in patients with bilateral carpal tunnel syndrome, biceps tendon rupture, and unexplained neuropathy suggest that CMR and ^{99m}Tc-PYP/DPD/HMDP scintigraphy likely have a clinical role. However, the panel chose a rating of "May Be Appropriate" because of the lack of definitive evidence and the need for more research to clarify the prevalence of cardiac amyloidosis and the role of imaging in these subgroups and other emerging high-risk cohorts (eg, transcutaneous aortic valve replacement,[5] hip and knee arthroplasty[38]).

Clinical Scenario #7: Prior Testing Suggestive of Cardiac Amyloidosis

In patients with an echocardiogram suggestive of cardiac amyloidosis, CMR was rated as "Appropriate" and likewise echocardiography was "Appropriate" with a suggestive CMR. ^{99m}Tc-PYP/DPD/HMDP scintigraphy was rated as "May Be Appropriate", because its use should be limited to suspected cases of ATTR cardiac amyloidosis. It should be noted that the most common clinical scenario is an older adult with an echo consistent with cardiac amyloidosis; in this group, the best test would likely be ^{99m}Tc-PYP/DPD/HMDP scintigraphy due to the high incidence of ATTR cardiac amyloidosis.

Summary

In Part 2 of this consensus statement, a panel of international experts have established the diagnostic criteria, clinical indications, and appropriate utilization of echocardiography, CMR, and radionuclide imaging for the assessment of cardiac amyloidosis. We hope that prospective clinical trials will validate these diagnostic criteria and appropriate utilization recommendations and will support guideline development.

Disclosures

All other contributors have nothing relevant to disclose.

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