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Contents

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Multi-modality imaging of cardiac amyloidosis: Contemporary update

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Abstract

Cardiac amyloidosis is a heterogeneous and challenging diagnostic disease with poor prognosis that is now being altered by introduction of new therapies. Echocardiography remains the first-line imaging tool, and when disease is suspected on echocardiography, cardiac magnetic resonance imaging and nuclear imaging play critical roles in the non-invasive diagnosis and evaluation of cardiac amyloidosis. Advances in multi-modality cardiac imaging allowing earlier diagnosis and initiation of novel therapies have significantly improved the outcomes in these patients. Cardiac imaging also plays important roles in the risk stratification of patients presenting with cardiac amyloidosis. In the current review, we provide a clinical and imaging focused update, and importantly outline the imaging protocols, diagnostic and prognostic utility of multimodality cardiac imaging in the assessment of cardiac amyloidosis.

Key words: Cardiac amyloidosis; Echocardiography; Cardiac magnetic resonance imaging; Nuclear imaging

Core tip: Cardiac amyloidosis remains a heterogeneous disease and diagnostic challenge with poor prognosis. The clinical perspectives from epidemiology, presentation, differential diagnoses and initial investigations are discussed. The key roles of the three cornerstone imaging modalities including echocardiography, magnetic resonance imaging and nuclear imaging are discussed pertaining to their techniques, protocols, findings, strengths and limitations. These are integrated into diagnostic criteria, followed by summaries of the novel therapeutics from recent clinical trials.

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INTRODUCTION

Cardiac amyloidosis is the abnormal extracellular deposition of pathological misfolded proteins, forming amyloid fibrils that accumulate in the heart causing progressive disease from myocardial toxicity, cellular dysfunction and death[1]. Over 30 different precursor proteins have been found to cause amyloidosis, with transthyretin (ATTR) and light chain (AL) amyloidosis being the most common[2,3]. Transthyretin, also known as pre-albumin, is made in the liver transporting thyroid hormone and vitamin A[3]. This is further divided into wild-type (senile-ATTRwt) and variant (hereditary-ATTRv) ATTR amyloidosis[3,4]. AL or primary amyloidosis on the other hand is a plasma cell clonal disorder with overproduction of immunoglobulin light chain fragments affecting multiple organs[1,3]. Although cardiac amyloidosis traditionally had poor prognosis with few treatment options, recent advances in multi-modality imaging have enabled earlier diagnosis and improved outcomes in conjunction with initiation of novel therapies[5]. This review aims to discuss the clinical utility of multi-modality cardiac imaging in the contemporary evaluation and management of cardiac amyloidosis. A specific focus is given to the nuclear medicine imaging techniques in cardiac amyloidosis.

CLINICAL CONSIDERATIONS

Epidemiology

Traditionally considered a rare condition, cardiac amyloidosis has become increasingly recognized due to increased awareness and improved cardiac imaging, and this is especially true for ATTR cardiac amyloidosis in selected elderly cohorts. One study found ATTRwt amyloidosis in 13% of 120 inpatients over 60 years of age with heart failure with preserved ejection fraction on nuclear imaging[6]. Another study found 12% of 43 aortic stenosis patients undergoing transcatheter aortic valve replacement having imaging findings suggestive of ATTRwt amyloidosis[7]. In addition, one study of 7733 mitral valve surgery patients also found 0.2% of unrecognized cardiac amyloidosis[8]. ATTRv is relatively less common, despite over 100 point mutations identified for the gene, and V1221I is the most common with 3%-4% of African Americans being heterozygous carriers[9]. AL cardiac amyloidosis is also very rare, with an incidence of approximately 1/100000 per year[10]. Whereas ATTR cardiac amyloidosis usually presents in patients 60 years of age or older and continues to increase in prevalence with aging populations, AL cardiac amyloidosis may present in younger patients.

Presentation

Diastolic heart failure (or heart failure with preserved ejection fraction) is the main manifestation for all forms of cardiac amyloidosis, which includes both left heart failure symptoms of dyspnea on exertion but also right heart failure symptoms of leg edema and ascites[11,12]. Notably, in a significant proportion of patients, the left ventricular systolic function and ejection fraction may be impaired in addition to diastolic dysfunction. Light-headedness and syncope can occur as a result of bradyarrhythmias or advanced atrioventricular block, while atrial fibrillation is also common. For ATTRv amyloidosis, two patterns have been observed, the first in the endemic foci of Portugal and Japan that manifests as early-onset disease with cardiac conduction disturbances often needing pacemaker implantation; the second pattern occurs in non-endemic areas, associated with later disease onset, and marked amyloid deposition and diastolic dysfunction[13]. These manifestations correlate with subendocardial long amyloid fibrils deposition leading to atrophy and degeneration in the first group, but diffuse myocardial short amyloid fibril deposition in the second group on histopathology[14,15]. Fatigue and weakness may be related to low cardiac output, while angina due to coronary involvement is rare.

More importantly, there are many extracardiac manifestations associated with cardiac amyloidosis, such as bilateral carpal tunnel syndrome (in all subtypes although most common in ATTRwt), low or normalization of previously high blood

pressure, spinal stenosis (especially ATTR subtypes), peripheral and autonomic neuropathy (especially AL and ATTRv), macroglossia and/or periorbital purpura (AL), proteinuria including nephrotic range (especially AL), jaw claudication, diarrhea and weight loss[4,11,16].

Signs on physical examination include pulmonary rales, elevated jugular venous pressure, leg edema, ascites, hepatic congestion and other extracardiac manifestations listed earlier. ATTR cardiac amyloidosis should also be considered in elderly patients with a new diagnosis of "hypertrophic cardiomyopathy" or low flow low gradient aortic stenosis especially with preserved EF and low stroke volume index[11].

Differential diagnoses

One of the challenges when evaluating patients for cardiac amyloidosis is the wide range of differential diagnoses that needs to be considered with similar clinical and imaging manifestations of increased left ventricular wall thickness[11,17]. Possibilities include hypertensive cardiomyopathy, aortic stenosis, hypertrophic cardiomyopathy, dilated cardiomyopathy, left ventricular non-compaction[18] and other reasons for heart failure with preserved ejection fraction. Other infiltrative diseases that can mimic cardiac amyloidosis include Anderson Fabry disease, Danon disease, sarcoidosis, hemochromatosis and Loeffler's endocarditis[19]. Differential diagnoses should be evaluated thoroughly, as part of the assessment for cardiac amyloidosis.

Non-imaging investigations

The three main non-imaging investigations for cardiac amyloidosis are electrocardiogram (ECG), blood tests and myocardial biopsy. Important ECG features include low to normal QRS voltage (less than what is expected from the degree of left ventricular wall thickness may be seen, and associated with adverse prognosis – Figure 1), and QS waves in two consecutive leads with pseudoinfarction pattern may also be present, although these typical findings may not be present in at least 50% of patients[20]. Both cardiac biomarkers N-terminal pro-b-type natriuretic peptide (NT-pro BNP) and troponin I and T are often chronically elevated in cardiac amyloidosis, so this diagnosis needs to be considered when these biomarkers are elevated after ruling out an acute coronary syndrome[21]. Serum free light chain assay is preferred as a more sensitive test to detect AL amyloidosis compared with serum or urine protein electrophoresis, with abnormal kappa-lambda ratio (low suggesting monoclonal lambda and high suggesting monoclonal kappa light chain excess), as opposed to elevated levels with normal ratio in renal failure[22]. Endomyocardial biopsy, albeit rarely utilized nowadays, remains the traditional gold standard for diagnostic confirmation of cardiac amyloidosis with near 100% sensitivity, identifying amyloid deposition extracellularly throughout the myocardium, though mainly subendocardial and diffuse for AL and patchy and transmural for ATTR[3]. Biopsies from other affected sites (for example: Fat pads, kidney, liver and bone marrow) can also be performed to evaluate for amyloidosis in these organs[1].

MULTIMODALITY IMAGING EVALUATION

Echocardiography

The echocardiographic protocol for evaluating cardiac amyloidosis is described in Table 1[5]. Based on this, it is mandatory to evaluate for left ventricular wall thickness, myocardial echogenicity, atrial size (and function), interatrial septum and valvular thickness, pericardial effusion, diastolic function including mitral inflow E and A wave ratio and deceleration times, tissue Doppler s', e' and a' velocities, and estimate pulmonary arterial systolic and right atrial pressures. Characterization of left ventricular longitudinal strain including the Bulls's eye plot by speckle-tracking echocardiography is also recommended. Imaging views and frame rates (at least 20 Hertz) should be optimized for two-dimensional and Doppler echocardiography. Overall interpretation of echocardiographic findings needs to be categorized as not suggestive, strongly suggestive and equivocal, and the latter two categories supporting further investigations. Integration of clinical presentation with electrocardiography, biomarker and other imaging findings is prudent, and comparison with prior echocardiographic findings is encouraged.

Figures 2 illustrates some characteristic echocardiographic findings. In the presence of increased left ventricular thickness with small or normal left ventricular size, and the absence of other clear causes, such as hypertension, advanced renal disease, and hypertrophic cardiomyopathy, cardiac amyloidosis needs to be considered[23]. The increased thickness can also affect the right ventricle, interatrial septum and heart valves, and pericardial effusion may also be present. Low voltage ECG in this setting
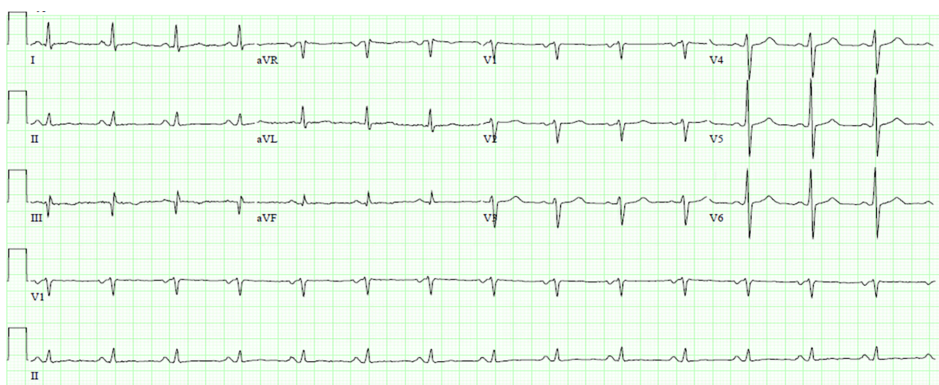
Figure 1 Characteristic electrocardiogram of cardiac amyloidosis demonstrating low QRS voltages.

is favors the presence of amyloid cardiac involvement. Left and right atrial dilation and dysfunction is common, as well as stasis and even thrombi in the left atrium and appendage[24]. Increased myocardial echogenicity may be seen, although this is non-specific, particularly with harmonic imaging and improved echocardiographic technology[23]. A range of diastolic dysfunction from mild to severe, with evidence of elevated left ventricular filling pressures is often seen[25]. Reduced left ventricular global longitudinal strain with normal ejection fraction is very common, and the typical "cherry-on-top" pattern is when there is impairment of basal segments strain compared to the relatively spared apex, quantitatively shown in one study as the relative apical longitudinal strain/average of basal and mid longitudinal strain ratio of at least 1 to be characteristic of cardiac amyloidosis[26]. Transesophageal and three-dimensional echocardiography do not generally add significantly to two-dimensional transthoracic echocardiography, unless there is improved spatial resolution. One utility however for transesophageal echocardiography is the exclusion of left atrial appendage thrombus which are not uncommon in patients with suspected amyloidosis with and without atrial fibrillation[27].

Beyond diagnosis, echocardiography also plays a role in risk evaluation of cardiac amyloidosis. Strain imaging plays an important role in prognostication, especially for AL cardiac amyloidosis. Reduced left ventricular systolic strain predicts all-cause mortality in patients with preserved left ventricular ejection fraction, as well as a higher relative regional strain ratio[28,29]. Similarly, impaired right ventricular strain was associated with worse survival in cardiac amyloidosis[30]. Other measures of left ventricular systolic function have also been shown to be associated with mortality including lower myocardial contractile fraction, mid-wall fractional shortening and Tei index[31-33]. Finally, left atrial size, left-sided valve thickening and pericardial effusions have been reported as poor prognostic markers[34-36]. Further research is required to integrate echocardiographic with clinical and biomarkers to create a multifactorial risk algorithm for cardiac amyloidosis[5].

Magnetic resonance imaging

The magnetic resonance imaging (MRI) protocol for assessing cardiac amyloidosis is listed in Table 2[5]. On the steady state free precession cine imaging with 2, 3 and 4-chamber and short-axis stack views, left ventricular size, wall thickness, ejection fraction, stroke volume and mass can all be evaluated[5,37]. Left and right atrial dimensions and function can also be evaluated, as well as the presence of pericardial effusion. Late gadolinium enhancement (LGE) imaging using phase-sensitive inversion recovery is preferred, with the same views as cine imaging. Native T1 pre-contrast and post-contrast mapping, should also be performed, usually at mid and basal short-axis and apical 4-chamber views. TI (inversion time scout) should be performed, and difficulty to null the myocardium over a range of inversion times may be observed. Similar to echocardiography, an overall interpretation of strongly suggestive, equivocal or not suggestive of cardiac amyloidosis should be made, as well as direct comparison with prior imaging evaluation.

Because of the tissue characterization utility of MRI, it is especially useful in the evaluation of increased left ventricular wall thickness, as well as identifying cardiac involvement of systemic amyloidosis[5]. Left ventricular ejection fraction may be preserved or impaired, but there is long-axis impairment with relative apical functional sparing and stroke volume index is often reduced. The thickened left ventricular wall is usually concentric, but may be asymmetric especially for the ATTR subtype[38]. Traditional LGE protocols have been challenging because of the difficulty

Table 1 Echocardiographic parameters to evaluate for cardiac amyloidosis, modified from expert consensus recommendations[5]

Parameters
Left ventricular size and ejection fraction
Left ventricular wall thickness
Myocardial echogenicity
Diastolic function
Left ventricular longitudinal strain (global and regional bull's eye distribution)
Atrial size and function
Interatrial septum
Estimated right ventricular systolic and right atrial pressures
Valve thickness
Pericardial effusion

nulling the myocardium in amyloidosis, which may be used to suggest this diagnosis, and T1 inversion scout is helpful to time delayed imaging[39]. This problem has been overcome by phase-sensitive inversion recovery sequences, and the pattern of distribution is often subendocardial (especially for AL subtype) or transmural (especially for ATTR subtype or advanced disease affecting both ventricles)[40]. A recent meta-analysis also reported 85% sensitivity and 92% specificity for LGE for diagnosing cardiac amyloidosis[41]. Another important study assessed the utility of LGE patterns in 46 AL and 51 ATTR cardiac amyloidosis patients[42]. They found that ATTR patients had more extensive LGE, with 90% of ATTR compared to 37% of AL patients having transmural LGE, and 100% of ATTR compared to 72% of AL patients had right ventricular LGE ($P < 0.001$ for both comparisons). More recently, T1 mapping pre-contrast as native T1 (with use of modified look-locker inversion recovery protocol) or post-contrast as extracellular cell volume (ECV representing infiltration) have helped the detection and quantification of infiltration for cardiac amyloidosis with high accuracy[43]. The reference ranges depend on the magnetic field strength, for example native T1 950 ± 21 ms and electrocardiogram 26% ± 4% for 1.5 Tesla scanners[44], and native T1 1139 ± 37 ms (males 1109 ± 73 ms and females 1139 ± 37 ms) for 3.0 Tesla scanners[45]. Notably, MRI cannot distinguish between ATTR and AL cardiac amyloidosis[5]. The cardiac MRI findings of a real-life case of ATTR cardiac amyloidosis are shown in Figure 3.

MRI also has important prognostic roles in cardiac amyloidosis. Similar to other cardiovascular diseases, LGE is associated with higher all-cause mortality in a meta-analysis[46]. Methods of systematic quantification of LGE for cardiac amyloidosis have not yet been developed, but this may help assess the degree of infiltration, progression and monitor response to treatment in the future. Higher native T1 mapping and extracellular volume when seen support the diagnosis of cardiac amyloidosis and are both also associated with worse prognosis[47]. T2 mapping for quantitatively assessing cardiac amyloidosis is also under investigation, with one study showing higher T2 representing edema to be associated with higher mortality[48].

Nuclear imaging
A relatively small number of radiotracers remain relevant in clinical practice today, predominantly 99mTc-phosphate derivatives[49]. Those include 99mTc-DPD (technetium-3,3-diphosphono-1,2-propanodicarboxylic acid), 99mTc-PYP (technetium pyrophosphate), and 99mTc-HMDP (technetium hydroxymethylene-diphosphonate). The mechanism of action of 99mTc-phosphate derivatives is hypothesized to be linked to the binding of calcium-rich TTR fibrils to phosphate-based tracers[50]. These radiotracers preferentially bind calcium rich ATTR-type rather than AL-type amyloid deposits, and thus have high sensitivity and specificity for ATTR amyloidosis. It is important to note that the documented sensitivity is dependent on studies of patients with advanced disease; the yield of 99mTc-phosphate derivatives in early stages of the disease is still unknown[5]. The practical acquisition protocols are available by the American Society of Nuclear Cardiology[5]. The patient is positioned supine with no pre-requisites of fasting or any other dietary preparations. The scan is done at rest and a planar image is acquired initially followed by a single-photon emission computerized tomography (SPECT) study; the dosages of radiotracers are 10-20 mCi (370-740 MBq) IV dose for 99mTc-DPD, 99mTc-PYP, and 99mTc-HMDP. The scan is done at
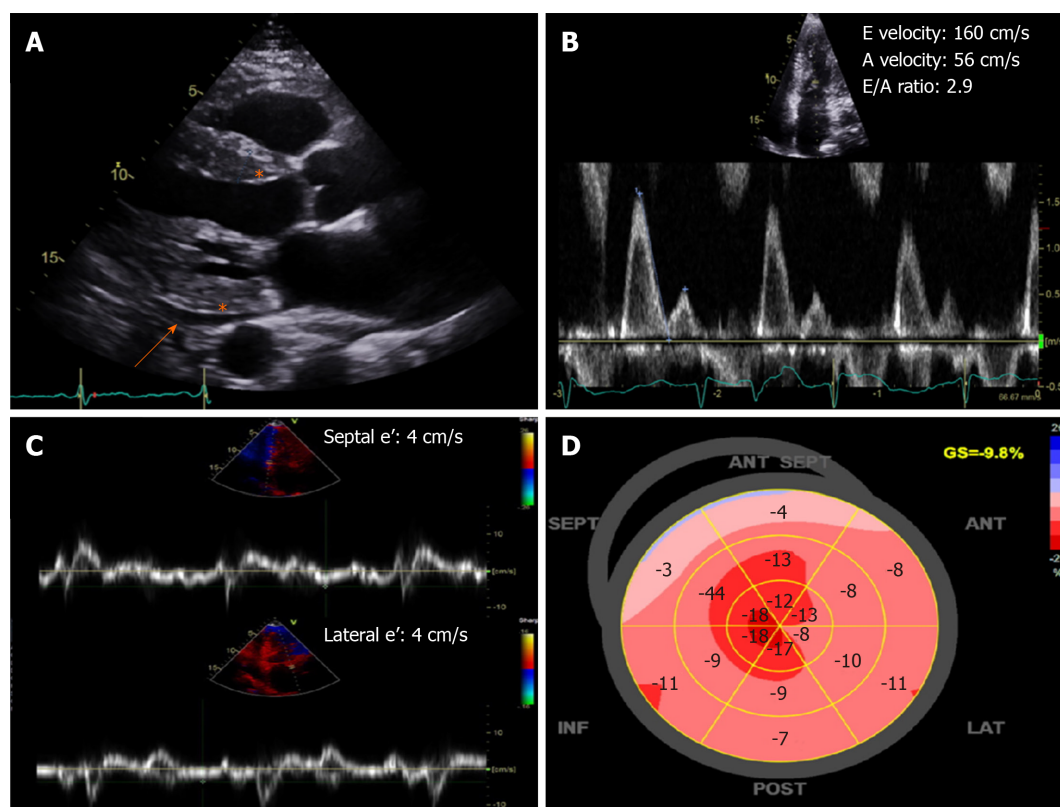
Figure 2 Characteristic echocardiography findings of cardiac amyloidosis. A: Increased left ventricular wall thickness and echogenicity (asterisk) with small effusion (orange arrow); B and C: Severe (restrictive) diastolic dysfunction with mitral inflow E/A ratio > 2.0 and low septal and lateral e' velocities by tissue Doppler; D: Bull's eye plot showing a "cherry-top" pattern of left ventricular peak systolic longitudinal strain, consistent with apical sparing pattern.

1 hour after the ^{99m}Tc-PYP administration (and a 3 hours acquisition is optional), while it is done at 2 or 3 hours after ^{99m}Tc-DPD/HMDP administration. The heart field is scanned mainly (Chest is optional). A 140 keV energy window is used with a low energy, high resolution collimator. The planar matrix is recommended at 256 × 256 while the SPECT is at least 64 × 64 with a 3.5-6.5 pixel size. For the planar parameters, a 90 degree detector configuration is used to acquire anterior and lateral images simultaneously with a magnification of 1.46 and image count duration of 750000. For the SPECT parameters, a 90 degrees detector configuration (with optional 180) is used with a 180 degree angular range (360 degree optional). No ECG gating is required. The magnification is 1.46 at 180 degrees and 1 at 360 degrees.

The interpretation of each study starts with the evaluation of the images, both planar and SPECT. A diffuse radiotracer uptake in the myocardium confirms the diagnosis of ATTR cardiac amyloidosis. It is important to take simultaneous anterior and lateral planar images, as well compare SPECT images to differentiate tracer uptake in the myocardium from activity from the blood pool that can be misconstrued as cardiac uptake, overlapping activity in sternum or ribs with fractures, and focal recent myocardial infarcts. If the tracer is visually detected in the myocardium on SPECT, the next step entails semi-quantitative grading (Figure 4). For the one-hour approach, an elliptical/circular region-of-interest (ROI) is drawn on the anterior planar images over the heart, avoiding sternal overlap and excluding adjacent lung. This ROI is mirrored over the contralateral lung to set a standard that nulls background and rib uptake. A heart-to-contralateral lung (H/CL) ratio is then calculated. For the three hour approach, a grading scale is used to compare tracer uptake relative to ribs; a grade zero has no myocardial uptake and normal bone uptake, grade 1: Myocardial uptake is less than the ribs, grade 2: Myocardial uptake is equal to the ribs, and grade 3: Myocardial uptake is greater than the ribs. Quantitative measures in identifying high diagnostic accuracy include a H/CL ratio of ≥ 1.5 on 1-h images for 99mTc tracers[51] and ≥ 1.3 on 3-h images in 99mTc-PYP studies[52].

The degree of cardiac uptake of 99mTc tracers correlates with overall mortality. A heart-to-whole body (H/WB) retention in 99mTc-DPD studies, and H/CL in 99mTc-PYP studies have been linked to patients' outcomes[53-55]. Combining the degree of uptake with other variables such as NYHA Class, NT-proBNP, and interventricular septal thickness improves the prognostic risk stratification. Current clinical practice

Table 2 Magnetic resonance imaging evaluation of cardiac amyloidosis, modified from expert consensus recommendations[5]

Protocol	Parameters
Steady state free precession cine imaging	Left ventricular size, stroke volume, ejection fraction, wall thickness, mass (without and with indexing), atrial size and function, pericardial effusion
Phase-sensitive inversion recovery for delayed contrast imaging	Late gadolinium enhancement
T1 imaging	Native T1 mapping pre-contrast, T1 inversion time scout, extracellular volume post-contrast
T2 imaging	T2 mapping, edema imaging

supports the use of 99mTc-derivatives to differentiate between ATTR and AL amyloidosis. The high specificity of 99mTc-PYP a negative blood and urine monoclonal protein is highly predictive of ATTR disease without the need of an endomyocardial biopsy. Furthermore, 99mTc-DPD may be able to discriminate the amyloid fibrils by length and distribution that distinguishes early- and late-onset ATTRv[56]. Genetic testing, however, remains imperative to differentiate mutant versus ATTRwt due to its screening implications for family members.

Positron emission tomography (PET) imaging is also showing some promise in the diagnosis of cardiac amyloidosis, but has yet to achieve standardized clinical practice protocols, as most of the experiences are single center-based and for research purposes. In general, targeted amyloid-binding 18F tracers are highly specific to AL and ATTR amyloid deposits with some variation. Commonly used and researched tracers include N-[methyl-(11)C]2-(4'-methylamino-phenyl)-6-hydroxybenzothiazole (11C-Pittsburgh compound B 11C-PiB), 18F-florbetapir, and 18F-florbetaben.

There are no standardized practice protocols endorsing the use of PET tracers yet. The assessment of PET images can be visual or through one of several indices of tracer uptake. Static images are reconstructed using data acquired throughout the study on established reconstructions PET software. Qualitative assessment of the images include myocardial standardized uptake value (SUV), target-to-background ratio, and myocardial retention index[57]. The quantitative analysis requires left ventricular (LV) contouring prior to identifying the uptake quantitatively. This is done by drawing base to apex LV contours of 10 mm thickness. A standard uptake value (SUV) of the myocardium can then be extracted from the image. The SUV of the adjacent descending thoracic aorta is also measured and averaged. A ratio of myocardium-to-blood SUV is calculated by dividing the maximal myocardial SUV to the averaged SUV of the descending aorta. The target-to-background index is calculated as the ratio of the mean LV myocardial SUV to the blood pool SUV over a set time during the study. Myocardial retention index is measured as mean LV SUV in each dynamic frame of the image divided by the integral of the blood pool 18F-florbetapir time–activity curve at that time point

Most importantly, PET tracers allow for quantitative assessment of amyloid burden. Also, PET images are usually fused with CT imaging or MRI improving reading accuracy. Using 18F-florbetapir and 18F-florbetaben, a target-to-background (myocardium to blood pool) ratio > 1.5 and a retention index of > 0.025/min separates cardiac amyloid patients from controls[58,59]. Recent studies on 11C-PiB have shown the potential of these tracers as independent predictors of clinical outcomes[60]. Due to their recent use, there are still limited data on the prognostic role of PET imaging. Table 3 summarizes the standard PET nuclear imaging acquisition and protocols for cardiac amyloidosis.

INTEGRATION OF MULTIMODALITY IMAGING ASSESSMENT

Diagnostic criteria
The latest diagnostic criteria for amyloidosis incorporating biopsy results, typical cardiac imaging features, biomarkers and blood tests for cardiac amyloidosis defined by the expert consensus from several international cardiology and cardiac imaging societies are summarized in Table 4[61]. Positive endomyocardial biopsy for cardiac amyloidosis with apple-green birefringence under polarized light with Congo red staining, immunohistochemistry or mass spectrometry typing alone is sufficient for diagnosing all subtypes of cardiac amyloidosis. Positive extracardiac biopsy of ATTR or AL cardiac amyloidosis requires typical cardiac imaging features to be also present to reach a diagnosis. For AL cardiac amyloidosis, abnormally elevated cardiac
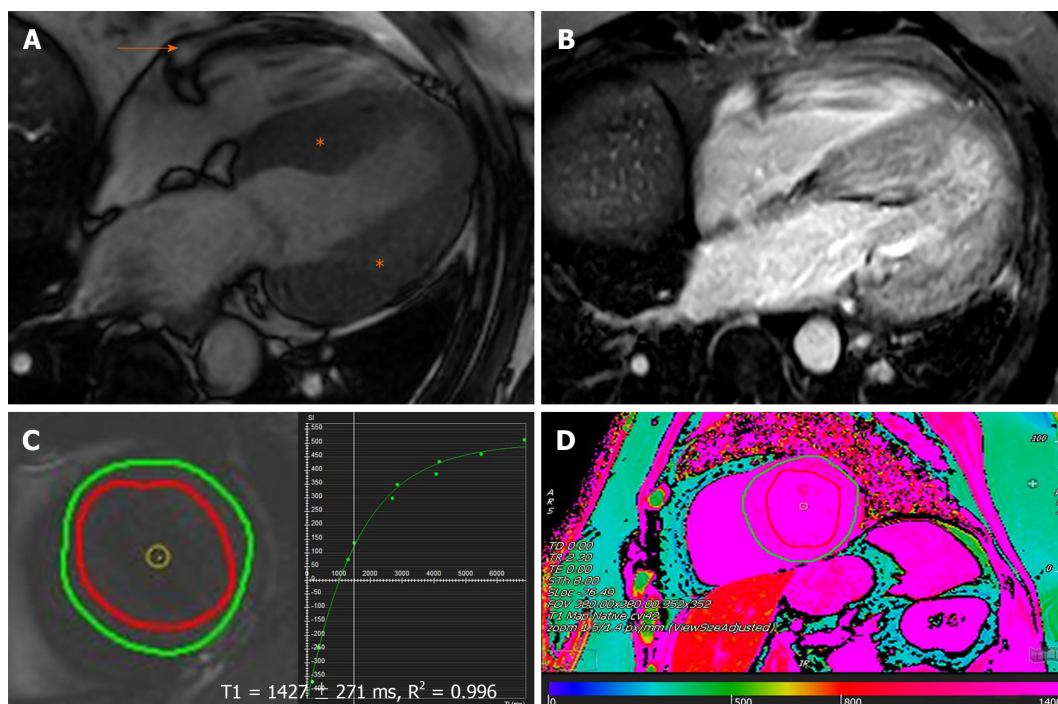
Figure 3 Characteristic magnetic resonance findings of cardiac amyloidosis. A: Increased left ventricular wall thickness (asterisk) with trivial pericardial effusion (orange arrow) on steady state free precession; B: Delayed enhancement imaging (phase sensitive inversion recovery sequence) demonstrating diffusely abnormal, transmural late gadolinium enhancement in the myocardium; C and D: Native T1-mapping (using the modified look-locker inversion recovery sequence) at left ventricular (C) basal level short-axis slice and (D) color map at left ventricular mid level short-axis, showing significantly elevated native T1-values and consistent with interstitial fibrosis. Note that the imaging acquisition in this example was performed using a dedicated 3.0 Tesla machine.

biomarkers NT-pro BNP or troponins with other causes excluded may be a substitute to typical cardiac imaging features for diagnosis. In addition, a clinical diagnosis of ATTR cardiac amyloidosis can also be made if nuclear imaging criteria are satisfied after negative serologic markers for AL; absence of clonal plasma cell process by serum free light chains and serum and urine immunofixation. Figure 5 presents a schematic of how multi-modality is used in the assessment and diagnosis of cardiac amyloidosis.

Strengths and weaknesses of imaging modalities

The advantages and disadvantages of echocardiography, MRI and nuclear imaging to evaluate cardiac amyloidosis are summarized in Table 5. Echocardiography remains the first line cardiac imaging investigation because of being readily available, safe, low cost, portable and has the most experience for the evaluation of diastolic function and myocardial deformation, but usually requires further confirmatory investigations[25,62]. MRI uniquely allows for tissue characterization and is the gold standard for chamber quantification because of high spatial resolution, although access, cost, claustrophobia, contrast use and metallic device may preclude from its use[37,62]. Nuclear imaging is also useful especially for identifying ATTR cardiac amyloidosis, however limitations include availability, cost, radiation exposure[5,63].

Novel therapeutics

The treatment for cardiac amyloidosis includes both treatment of heart failure and other cardiac complications, and treatment of the underlying amyloid infiltrative disease[11]. The latter is markedly different between ATTR and AL cardiac amyloidosis, therefore accurate classification by multi-modality imaging and other investigations are critical. Traditionally, chemotherapy regimens and stem cell transplantation are the mainstay treatments for AL amyloidosis eliminating plasma cell clones central to its pathophysiology to alter the natural history with poor prognosis[64]. The recent novel therapeutics in ATTR cardiac amyloidosis deserve special mention. Tafamidis is a drug that binds transthyretin to reduce amyloidogenesis, and in a randomized trial of 441 patients significantly reduced both all-cause mortality and cardiovascular hospitalization by 30%-32% while slowing functional and quality of life decline, becoming the new preferred therapy for ATTR amyloidosis[65]. Inotersen is a oligonucleotide drug blocking hepatic transthyretin synthesis, and in a randomized controlled trial of 172 patients improved the course of
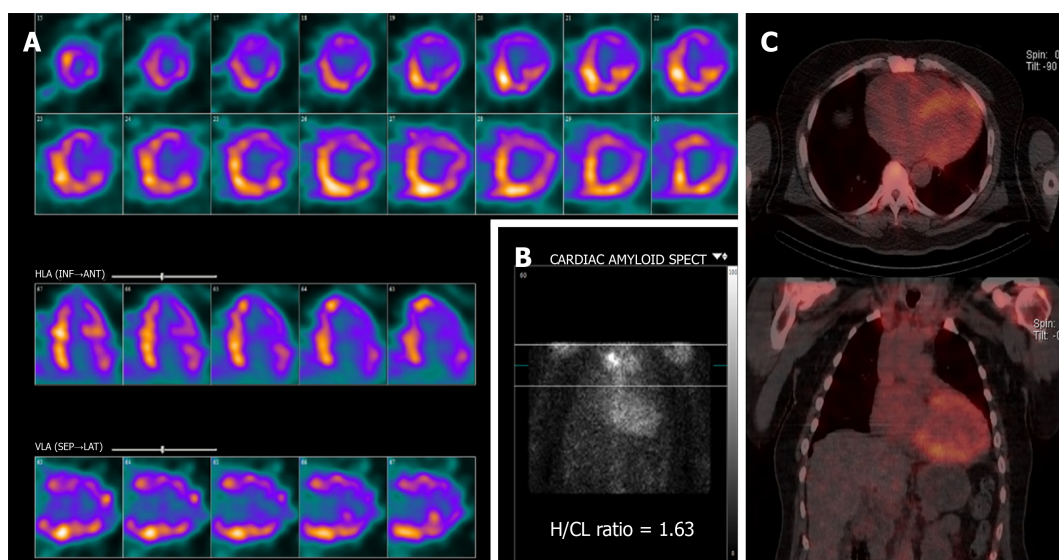
Figure 4 Tc-99m-Pyrophosphate SPECT of the chest with computed tomography attenuation correction at 3 h after intravenous injection of Tc-99m Pyrophosphate. A: Single-photon emission computerized tomography (SPECT) exhibits diffuse uptake pattern; B: Planar image depicts by visual comparison to bone a Grade 2 uptake (equal to rib uptake). The calculated H/CL ratio is measured at 1.63; C: SPECT/Computed tomography fusion showing distribution of the increased cardiac uptake. SPECT: Single-photon emission computerized tomography; H/CL: Heart-to-contralateral lung.

neurologic disease and quality of life in ATTRv amyloidosis[66]. Patisiran is a RNA interference drug also reducing hepatic transthyretin production which ins another randomized controlled trial of 225 patients similarly improved functional capacity and quality of life[67]. Of note, the management and novel therapies for cardiac amyloidosis is not the focus of this review.

CONCLUSION

Significant advances have occurred in multimodality cardiac imaging for assessing cardiac amyloidosis. Echocardiography, MRI and nuclear imaging all play important and complementary roles in this clinical scenario. Echocardiography is first-line for chamber quantification, assessing diastolic function and myocardial deformation. MRI uniquely offers tissue characterization and quantification of infiltration on top of chamber quantification. Nuclear imaging is the only currently available non-invasive modality able to distinguish ATTR from AL cardiac amyloidosis. Each modality also plays a role in risk stratification for adverse outcomes. Contemporary imaging plays a central role in helping improve the diagnosis and management outcomes of cardiac amyloidosis. It remains to be seen whether we can use these non-invasive imaging tools to follow disease progression/regression after initiation of novels therapies especially with ATTR cardiac amyloidosis.

Table 3 Utilized acquisition parameters for ^{11}C-PiB, ^{18}F florbetapir, and ^{18}F florbetaben studies for cardiac amyloidosis[50-52]

Imaging considerations	Parameters
Patient and equipment preparation	
Patient preparation	No prerequisites, no fasting
Position	Supine arms above shoulder or supported
Scan	Rest scan
Dose	^{11}C-PiB 10-20 mCi (370-740 MBq) IV[50]
	[18]F florbetapir 6 mCi (222 MBq) IV[51]
	[18]F florbetaben 0.1 mCi/kg (4 MBq/kg) IV[52]
Time from injection to acquisition	^{11}C-PiB 30 min[50]
	[18]F florbetapir continuous over 60 min[51]
	[18]F florbetaben continuous over 80 min[52]
Scan parameters	
Field of view	Heart; Chest
Image type	Low-dose (10 mA, 120 kVp, free tidal breathing) CT scout scan
	Low-dose CT transmission scan (10 mA, 120 kVp, free tidal breathing) over the heart
	Emission scan 2D 40-60 mCi (1480-2220 MBq)
	Emission scan 3D 10-20 mCi (370-740 MBq)
Matrix	128 × 128-400 × 400
Reconstruction	Filtered back projection or iterative reconstruction

CT: Computed tomography.

Table 4 Contemporary diagnostic criteria for cardiac amyloidosis, modified from expert consensus recommendations[61]

Category	Criteria
Endomyocardial biopsy	Apple-green birefringence with Congo red staining and polarized light, immunohistochemistry and/or mass spectrometry typing confirmed
Extracardiac biopsy	ATTR: Biopsy proven and typical imaging findings
	AL: biopsy proven and typical imaging features or abnormal cardiac biomarkers (N-terminus B-type natriuretic peptide or troponins if other causes excluded)
Non-biopsy (or ATTR)	Grade 2 or 3 myocardial uptake of radiotracer
	Serum free light chains, serum and urine immune-fixation not finding clonal plasma cell process
	Typical imaging findings
Typical imaging findings: echocardiography	Left ventricular wall thickness > 12mm
	Relative apical sparing of left ventricular longitudinal strain ratio (apical average/basal and mid average > 1)
	Grade 2 or higher diastolic dysfunction
Typical imaging findings: magnetic resonance imaging	Left ventricular wall thickness > upper limit normal for sex
	Global extracellular volume > 0.40
	Abnormal gadolinium kinetics, myocardial nulling prior to blood pool nulling or difficulty in nulling the myocardium because of diffuse amyloid infiltration
	Diffuse, subendocardial or patchy late gadolinium enhancement patterns may be observed
Typical imaging findings: Positron emission tomography	^{18}F-florbetapir or ^{18}F-florbetabem
	Left ventricular myocardium to blood pool ratio > 1.5
	Retention index > 0.030/min

ATTR: Transthyretin amyloidosis; AL: Light chain amyloidosis.

Table 5 Strengths and limitations of each imaging modality for assessing cardiac amyloidosis

Modality	Echocardiography	Magnetic resonance imaging	Nuclear imaging
Strengths	Availability and portable	Lack of radiation	Distinguishing between AL/ATTR
	Low cost	High spatial resolution	
	Lack of radiation	Chamber quantification	
	Lack of contrast	Tissue characterization	
	Chamber quantification	Quantifying myocardial fibrosis	
	Diastolic function		
	Strain		
Weaknesses	Variable spatial resolution	Higher cost	Higher cost
	Low specificity	Availability may be limited	Availability may be limited
	No tissue characterization	Gadolinium-based contrast administration	Radiation exposure
	Not distinguish AL/ATTR	Claustrophobia	
	Not able to assess and quantify myocardial fibrosis	Metallic device	
		Not able to distinguish between AL/ATTR	

AL: Light chain amyloidosis; ATTR: Transthyretin amyloidosis.

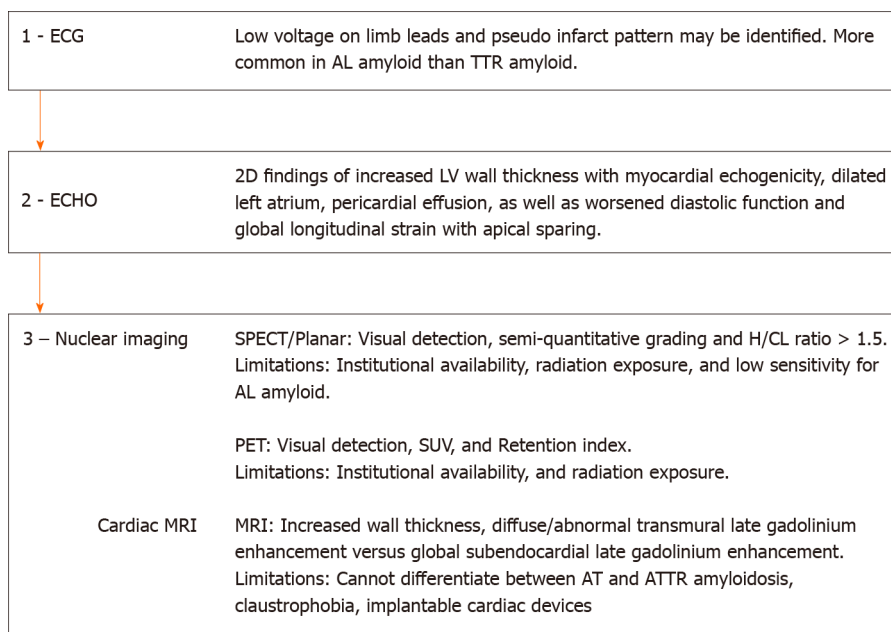| 1 - ECG	Low voltage on limb leads and pseudo infarct pattern may be identified. More common in AL amyloid than TTR amyloid.
2 - ECHO	2D findings of increased LV wall thickness with myocardial echogenicity, dilated left atrium, pericardial effusion, as well as worsened diastolic function and global longitudinal strain with apical sparing.
3 – Nuclear imaging	SPECT/Planar: Visual detection, semi-quantitative grading and H/CL ratio > 1.5. Limitations: Institutional availability, radiation exposure, and low sensitivity for AL amyloid. PET: Visual detection, SUV, and Retention index. Limitations: Institutional availability, and radiation exposure.
Cardiac MRI	MRI: Increased wall thickness, diffuse/abnormal transmural late gadolinium enhancement versus global subendocardial late gadolinium enhancement. Limitations: Cannot differentiate between AT and ATTR amyloidosis, claustrophobia, implantable cardiac devices

Figure 5 Schematic diagram of the stepwise use of electrocardiogram and multi-modality imaging in the diagnosis and evaluation of cardiac amyloidosis. ECG: Electrocardiogram; AL: Light chain amyloidosis; TTR: Transthyretin; ECHO: Echocardiogram; SPECT: Single-photon emission computerized tomography; H/CL: Heart-to-contralateral lung; PET: Positron-emission tomography; SUV: Standardized uptake value; MRI: Magnetic-resonance imaging; ATTR: Transthyretin amyloidosis.

REFERENCES

1   **Merlini G**, Bellotti V. Molecular mechanisms of amyloidosis. *N Engl J Med* 2003; **349**: 583-596 [PMID: 12904524 DOI: 10.1056/NEJMra023144]
2   **Fontana M**, Ćorović A, Scully P, Moon JC. Myocardial Amyloidosis: The Exemplar Interstitial Disease. *JACC Cardiovasc Imaging* 2019; **12**: 2345-2356 [PMID: 31422120 DOI: 10.1016/j.jcmg.2019.06.023]
3   **Maleszewski JJ**. Cardiac amyloidosis: pathology, nomenclature, and typing. *Cardiovasc Pathol* 2015; **24**: 343-350 [PMID: 26361138 DOI: 10.1016/j.carpath.2015.07.008]
4   **Koike H**, Katsuno M. Ultrastructure in Transthyretin Amyloidosis: From Pathophysiology to Therapeutic Insights. *Biomedicines* 2019; **7**: 11 [PMID: 30764529 DOI: 10.3390/biomedicines7010011]
5   **Dorbala S**, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA, Fontana M, Gheysens O, Gillmore JD, Glaudemans AWJM, Hanna MA, Hazenberg BPC, Kristen AV, Kwong RY, Maurer MS, Merlini G, Miller EJ, Moon JC, Murthy VL, Quarta CC, Rapezzi C, Ruberg FL, Shah SJ, Slart RHJA, Verberne HJ,

Bourque JM. 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**: 2065-2123 [PMID: 31468376 DOI: 10.1007/s12350-019-01760-6]

6   **González-López E**, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, Bornstein B, Salas C, Lara-Pezzi E, Alonso-Pulpon L, Garcia-Pavia P. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J* 2015; **36**: 2585-2594 [PMID: 26224076 DOI: 10.1093/eurheartj/ehv338]

7   **Longhi S**, Lorenzini M, Gagliardi C, Milandri A, Marzocchi A, Marrozzini C, Saia F, Ortolani P, Biagini E, Guidalotti PL, Leone O, Rapezzi C. Coexistence of Degenerative Aortic Stenosis and Wild-Type Transthyretin-Related Cardiac Amyloidosis. *JACC Cardiovasc Imaging* 2016; **9**: 325-327 [PMID: 26189123 DOI: 10.1016/j.jcmg.2015.04.012]

8   **Murtagh B**, Hammill SC, Gertz MA, Kyle RA, Tajik AJ, Grogan M. Electrocardiographic findings in primary systemic amyloidosis and biopsy-proven cardiac involvement. *Am J Cardiol* 2005; **95**: 535-537 [PMID: 15695149 DOI: 10.1016/j.amjcard.2004.10.028]

9   **Buxbaum J**, Jacobson DR, Tagoe C, Alexander A, Kitzman DW, Greenberg B, Thaneemit-Chen S, Lavori P. Transthyretin V122I in African Americans with congestive heart failure. *J Am Coll Cardiol* 2006; **47**: 1724-1725 [PMID: 16631014 DOI: 10.1016/j.jacc.2006.01.042]

10   **Wechalekar AD**, Gillmore JD, Hawkins PN. Systemic amyloidosis. *Lancet* 2016; **387**: 2641-2654 [PMID: 26719234 DOI: 10.1016/S0140-6736(15)01274-X]

11   **Donnelly JP**, Hanna M. Cardiac amyloidosis: An update on diagnosis and treatment. *Cleve Clin J Med* 2017; **84**: 12-26 [PMID: 29257735 DOI: 10.3949/ccjm.84.s3.02]

12   **Siddiqi OK**, Ruberg FL. Cardiac amyloidosis: An update on pathophysiology, diagnosis, and treatment. *Trends Cardiovasc Med* 2018; **28**: 10-21 [PMID: 28739313 DOI: 10.1016/j.tcm.2017.07.004]

13   **Koike H**, Misu K, Ikeda S, Ando Y, Nakazato M, Ando E, Yamamoto M, Hattori N, Sobue G; Study Group for Hereditary Neuropathy in Japan. Type I (transthyretin Met30) familial amyloid polyneuropathy in Japan: early- vs late-onset form. *Arch Neurol* 2002; **59**: 1771-1776 [PMID: 12433265 DOI: 10.1001/archneur.59.11.1771]

14   **Koike H**, Misu K, Sugiura M, Iijima M, Mori K, Yamamoto M, Hattori N, Mukai E, Ando Y, Ikeda S, Sobue G. Pathology of early- vs late-onset TTR Met30 familial amyloid polyneuropathy. *Neurology* 2004; **63**: 129-138 [PMID: 15249622 DOI: 10.1212/01.wnl.0000132966.36437.12]

15   **Bergström J**, Gustavsson A, Hellman U, Sletten K, Murphy CL, Weiss DT, Solomon A, Olofsson BO, Westermark P. Amyloid deposits in transthyretin-derived amyloidosis: cleaved transthyretin is associated with distinct amyloid morphology. *J Pathol* 2005; **206**: 224-232 [PMID: 15810051 DOI: 10.1002/path.1759]

16   **Dubrey SW**, Cha K, Anderson J, Chamarthi B, Reisinger J, Skinner M, Falk RH. The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. *QJM* 1998; **91**: 141-157 [PMID: 9578896 DOI: 10.1093/qjmed/91.2.141]

17   **Kubo T**, Kitaoka H. Imaging of Left Ventricular Hypertrophy: a Practical Utility for Differential Diagnosis and Assessment of Disease Severity. *Curr Cardiol Rep* 2017; **19**: 65 [PMID: 28639223 DOI: 10.1007/s11886-017-0875-5]

18   **Celebi AS**, Gulel O, Cicekcioglu H, Celebi OO, Ulusoy V. Isolated noncompaction of the left ventricular myocardium complicated by thromboembolic cerebrovascular accident in a patient with essential thrombocythemia. *Int J Cardiol* 2008; **128**: e22-e24 [PMID: 17669523 DOI: 10.1016/j.ijcard.2007.04.160]

19   **Gulel O**, Camlidag I, Elmali M. Successful Medical Management of a Rare Loeffler Endocarditis Case. *Korean Circ J* 2018; **48**: 655-657 [PMID: 29968439 DOI: 10.4070/kcj.2017.0348]

20   **Cyrille NB**, Goldsmith J, Alvarez J, Maurer MS. Prevalence and prognostic significance of low QRS voltage among the three main types of cardiac amyloidosis. *Am J Cardiol* 2014; **114**: 1089-1093 [PMID: 25212550 DOI: 10.1016/j.amjcard.2014.07.026]

21   **Kristen AV**, Maurer MS, Rapezzi C, Mundayat R, Suhr OB, Damy T; THAOS investigators. Impact of genotype and phenotype on cardiac biomarkers in patients with transthyretin amyloidosis - Report from the Transthyretin Amyloidosis Outcome Survey (THAOS). *PLoS One* 2017; **12**: e0173086 [PMID: 28384285 DOI: 10.1371/journal.pone.0173086]

22   **Maurer MS**, Elliott P, Comenzo R, Semigran M, Rapezzi C. Addressing Common Questions Encountered in the Diagnosis and Management of Cardiac Amyloidosis. *Circulation* 2017; **135**: 1357-1377 [PMID: 28373528 DOI: 10.1161/CIRCULATIONAHA.116.024438]

23   **Gertz MA**, Comenzo R, Falk RH, Fermand JP, Hazenberg BP, Hawkins PN, Merlini G, Moreau P, Ronco P, Sanchorawala V, Sezer O, Solomon A, Grateau G. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. *Am J Hematol* 2005; **79**: 319-328 [PMID: 16044444 DOI: 10.1002/ajh.20381]

24   **Nochioka K**, Quarta CC, Claggett B, Roca GQ, Rapezzi C, Falk RH, Solomon SD. Left atrial structure and function in cardiac amyloidosis. *Eur Heart J Cardiovasc Imaging* 2017; **18**: 1128-1137 [PMID: 28637305 DOI: 10.1093/ehjci/jex097]

25   **Nagueh SF**, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009; **22**: 107-133 [PMID: 19187853 DOI: 10.1016/j.echo.2008.11.023]

26   **Phelan D**, Collier P, Thavendiranathan P, Popović ZB, Hanna M, Plana JC, Marwick TH, Thomas JD. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. *Heart* 2012; **98**: 1442-1448 [PMID: 22865865 DOI: 10.1136/heartjnl-2012-302353]

27   **Donnellan E**, Elshazly MB, Vakamudi S, Wazni OM, Cohen JA, Kanj M, Hanna M, Baranowski B, Saliba W, Jaber W. No Association Between CHADS-VASc Score and Left Atrial Appendage Thrombus in Patients With Transthyretin Amyloidosis. *JACC Clin Electrophysiol* 2019; **5**: 1473-1474 [PMID: 31857048 DOI: 10.1016/j.jacep.2019.10.013]

28   **Barros-Gomes S**, Williams B, Nhola LF, Grogan M, Maalouf JF, Dispenzieri A, Pellikka PA, Villarraga HR. Prognosis of Light Chain Amyloidosis With Preserved LVEF: Added Value of 2D Speckle-Tracking Echocardiography to the Current Prognostic Staging System. *JACC Cardiovasc Imaging* 2017; **10**: 398-407 [PMID: 27639764 DOI: 10.1016/j.jcmg.2016.04.008]

29   **Senapati A**, Sperry BW, Grodin JL, Kusunose K, Thavendiranathan P, Jaber W, Collier P, Hanna M, Popovic ZB, Phelan D. Prognostic implication of relative regional strain ratio in cardiac amyloidosis.

Heart 2016; **102**: 748-754 [PMID: 26830665 DOI: 10.1136/heartjnl-2015-308657]

30   **Bellavia D**, Pellikka PA, Dispenzieri A, Scott CG, Al-Zahrani GB, Grogan M, Pitrolo F, Oh JK, Miller FA Jr. Comparison of right ventricular longitudinal strain imaging, tricuspid annular plane systolic excursion, and cardiac biomarkers for early diagnosis of cardiac involvement and risk stratification in primary systematic (AL) amyloidosis: a 5-year cohort study. *Eur Heart J Cardiovasc Imaging* 2012; **13**: 680-689 [PMID: 22307866 DOI: 10.1093/ehjci/jes009]

31   **Tendler A**, Helmke S, Teruya S, Alvarez J, Maurer MS. The myocardial contraction fraction is superior to ejection fraction in predicting survival in patients with AL cardiac amyloidosis. *Amyloid* 2015; **22**: 61-66 [PMID: 25510353 DOI: 10.3109/13506129.2014.994202]

32   **Perlini S**, Salinaro F, Musca F, Mussinelli R, Boldrini M, Raimondi A, Milani P, Foli A, Cappelli F, Perfetto F, Palladini G, Rapezzi C, Merlini G. Prognostic value of depressed midwall systolic function in cardiac light-chain amyloidosis. *J Hypertens* 2014; **32**: 1121-31; discussion 1131 [PMID: 24509117 DOI: 10.1097/HJH.0000000000000120]

33   **Tei C**, Dujardin KS, Hodge DO, Kyle RA, Tajik AJ, Seward JB. Doppler index combining systolic and diastolic myocardial performance: clinical value in cardiac amyloidosis. *J Am Coll Cardiol* 1996; **28**: 658-664 [PMID: 8772753 DOI: 10.1016/0735-1097(96)00202-1]

34   **Mohty D**, Pibarot P, Dumesnil JG, Darodes N, Lavergne D, Echahidi N, Virot P, Bordessoule D, Jaccard A. Left atrial size is an independent predictor of overall survival in patients with primary systemic amyloidosis. *Arch Cardiovasc Dis* 2011; **104**: 611-618 [PMID: 22152513 DOI: 10.1016/j.acvd.2011.10.004]

35   **Mohty D**, Pradel S, Magne J, Fadel B, Boulogne C, Petitalot V, Raboukhi S, Darodes N, Damy T, Aboyans V, Jaccard A. Prevalence and prognostic impact of left-sided valve thickening in systemic light-chain amyloidosis. *Clin Res Cardiol* 2017; **106**: 331-340 [PMID: 27933393 DOI: 10.1007/s00392-016-1058-x]

36   **Damy T**, Jaccard A, Guellich A, Lavergne D, Galat A, Deux JF, Hittinger L, Dupuis J, Frenkel V, Rigaud C, Plante-Bordeneuve V, Bodez D, Mohty D. Identification of prognostic markers in transthyretin and AL cardiac amyloidosis. *Amyloid* 2016; **23**: 194-202 [PMID: 27647161 DOI: 10.1080/13506129.2016.1221815]

37   **Kramer CM**, Barkhausen J, Flamm SD, Kim RJ, Nagel E; Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized Protocols. Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update. *J Cardiovasc Magn Reson* 2013; **15**: 91 [PMID: 24103764 DOI: 10.1186/1532-429X-15-91]

38   **Martinez-Naharro A**, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS, Kotecha T, Francis R, Hutt DF, Rezk T, Rosmini S, Quarta CC, Whelan CJ, Kellman P, Gillmore JD, Moon JC, Hawkins PN, Fontana M. Magnetic Resonance in Transthyretin Cardiac Amyloidosis. *J Am Coll Cardiol* 2017; **70**: 466-477 [PMID: 28728692 DOI: 10.1016/j.jacc.2017.05.053]

39   **Pandey T**, Jambhekar K, Shaikh R, Lensing S, Viswamitra S. Utility of the inversion scout sequence (TI scout) in diagnosing myocardial amyloid infiltration. *Int J Cardiovasc Imaging* 2013; **29**: 103-112 [PMID: 22527255 DOI: 10.1007/s10554-012-0042-4]

40   **Fontana M**, Pica S, Reant P, Abdel-Gadir A, Treibel TA, Banypersad SM, Maestrini V, Barcella W, Rosmini S, Bulluck H, Sayed RH, Patel K, Mamhood S, Bucciarelli-Ducci C, Whelan CJ, Herrey AS, Lachmann HJ, Wechalekar AD, Manisty CH, Schelbert EB, Kellman P, Gillmore JD, Hawkins PN, Moon JC. Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. *Circulation* 2015; **132**: 1570-1579 [PMID: 26362631 DOI: 10.1161/CIRCULATIONAHA.115.016567]

41   **Zhao L**, Tian Z, Fang Q. Diagnostic accuracy of cardiovascular magnetic resonance for patients with suspected cardiac amyloidosis: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 2016; **16**: 129 [PMID: 27267362 DOI: 10.1186/s12872-016-0311-6]

42   **Dungu JN**, Valencia O, Pinney JH, Gibbs SD, Rowczenio D, Gilbertson JA, Lachmann HJ, Wechalekar A, Gillmore JD, Whelan CJ, Hawkins PN, Anderson LJ. CMR-based differentiation of AL and ATTR cardiac amyloidosis. *JACC Cardiovasc Imaging* 2014; **7**: 133-142 [PMID: 24412186 DOI: 10.1016/j.jcmg.2013.08.015]

43   **Karamitsos TD**, Piechnik SK, Banypersad SM, Fontana M, Ntusi NB, Ferreira VM, Whelan CJ, Myerson SG, Robson MD, Hawkins PN, Neubauer S, Moon JC. Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis. *JACC Cardiovasc Imaging* 2013; **6**: 488-497 [PMID: 23498672 DOI: 10.1016/j.jcmg.2012.11.013]

44   **Dabir D**, Child N, Kalra A, Rogers T, Gebker R, Jabbour A, Plein S, Yu CY, Otton J, Kidambi A, McDiarmid A, Broadbent D, Higgins DM, Schnackenburg B, Foote L, Cummins C, Nagel E, Puntmann VO. Reference values for healthy human myocardium using a T1 mapping methodology: results from the International T1 Multicenter cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson* 2014; **16**: 69 [PMID: 25384607 DOI: 10.1186/s12968-014-0069-x]

45   **Roy C**, Slimani A, de Meester C, Amzulescu M, Pasquet A, Vancraeynest D, Vanoverschelde JL, Pouleur AC, Gerber BL. Age and sex corrected normal reference values of T1, T2 T2* and ECV in healthy subjects at 3T CMR. *J Cardiovasc Magn Reson* 2017; **19**: 72 [PMID: 28934962 DOI: 10.1186/s12968-017-0371-5]

46   **Raina S**, Lensing SY, Nairooz RS, Pothineni NV, Hakeem A, Bhatti S, Pandey T. Prognostic Value of Late Gadolinium Enhancement CMR in Systemic Amyloidosis. *JACC Cardiovasc Imaging* 2016; **9**: 1267-1277 [PMID: 27568115 DOI: 10.1016/j.jcmg.2016.01.036]

47   **Banypersad SM**, Fontana M, Maestrini V, Sado DM, Captur G, Petrie A, Piechnik SK, Whelan CJ, Herrey AS, Gillmore JD, Lachmann HJ, Wechalekar AD, Hawkins PN, Moon JC. T1 mapping and survival in systemic light-chain amyloidosis. *Eur Heart J* 2015; **36**: 244-251 [PMID: 25411195 DOI: 10.1093/eurheartj/ehu444]

48   **Kotecha T**, Martinez-Naharro A, Treibel TA, Francis R, Nordin S, Abdel-Gadir A, Knight DS, Zumbo G, Rosmini S, Maestrini V, Bulluck H, Rakhit RD, Wechalekar AD, Gilbertson J, Sheppard MN, Kellman P, Gillmore JD, Moon JC, Hawkins PN, Fontana M. Myocardial Edema and Prognosis in Amyloidosis. *J Am Coll Cardiol* 2018; **71**: 2919-2931 [PMID: 29929616 DOI: 10.1016/j.jacc.2018.03.536]

49   **Aljaroudi WA**, Desai MY, Tang WH, Phelan D, Cerqueira MD, Jaber WA. Role of imaging in the diagnosis and management of patients with cardiac amyloidosis: state of the art review and focus on emerging nuclear techniques. *J Nucl Cardiol* 2014; **21**: 271-283 [PMID: 24347127 DOI: 10.1007/s12350-013-9800-5]

50   **Chen W**, Dilsizian V. Molecular imaging of amyloidosis: will the heart be the next target after the brain?

Curr Cardiol Rep 2012; **14**: 226-233 [PMID: 22193845 DOI: 10.1007/s11886-011-0239-5]

51 **Gillmore JD**, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, Wechalekar AD, Berk JL, Quarta CC, Grogan M, Lachmann HJ, Bokhari S, Castano A, Dorbala S, Johnson GB, Glaudemans AW, Rezk T, Fontana M, Palladini G, Milani P, Guidalotti PL, Flatman K, Lane T, Vonberg FW, Whelan CJ, Moon JC, Ruberg FL, Miller EJ, Hutt DF, Hazenberg BP, Rapezzi C, Hawkins PN. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. *Circulation* 2016; **133**: 2404-2412 [PMID: 27143678 DOI: 10.1161/CIRCU-LATIONAHA.116.021612]

52 **Castaño A**, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, Rubin J, Chiuzan C, Nazif T, Vahl T, George I, Kodali S, Leon MB, Hahn R, Bokhari S, Maurer MS. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J* 2017; **38**: 2879-2887 [PMID: 29019612 DOI: 10.1093/eurheartj/ehx350]

53 **Rapezzi C**, Quarta CC, Guidalotti PL, Pettinato C, Fanti S, Leone O, Ferlini A, Longhi S, Lorenzini M, Reggiani LB, Gagliardi C, Gallo P, Villani C, Salvi F. Role of (99m)Tc-DPD scintigraphy in diagnosis and prognosis of hereditary transthyretin-related cardiac amyloidosis. *JACC Cardiovasc Imaging* 2011; **4**: 659-670 [PMID: 21679902 DOI: 10.1016/j.jcmg.2011.03.016]

54 **Castano A**, Haq M, Narotsky DL, Goldsmith J, Weinberg RL, Morgenstern R, Pozniakoff T, Ruberg FL, Miller EJ, Berk JL, Dispenzieri A, Grogan M, Johnson G, Bokhari S, Maurer MS. Multicenter Study of Planar Technetium 99m Pyrophosphate Cardiac Imaging: Predicting Survival for Patients With ATTR Cardiac Amyloidosis. *JAMA Cardiol* 2016; **1**: 880-889 [PMID: 27557400 DOI: 10.1001/jamacardio.2016.2839]

55 **Vranian MN**, Sperry BW, Hanna M, Hachamovitch R, Ikram A, Brunken RC, Jaber WA. Technetium pyrophosphate uptake in transthyretin cardiac amyloidosis: Associations with echocardiographic disease severity and outcomes. *J Nucl Cardiol* 2018; **25**: 1247-1256 [PMID: 28050864 DOI: 10.1007/s12350-016-0768-9]

56 **Suhr OB**, Wixner J, Anan I, Lundgren HE, Wijayatunga P, Westermark P, Ihse E. Amyloid fibril composition within hereditary Val30Met (p. Val50Met) transthyretin amyloidosis families. *PLoS One* 2019; **14**: e0211983 [PMID: 30811423 DOI: 10.1371/journal.pone.0211983]

57 **Dorbala S**, Vangala D, Semer J, Strader C, Bruyere JR Jr, Di Carli MF, Moore SC, Falk RH. Imaging cardiac amyloidosis: a pilot study using ¹F-florbetapir positron emission tomography. *Eur J Nucl Med Mol Imaging* 2014; **41**: 1652-1662 [PMID: 24841414 DOI: 10.1007/s00259-014-2787-6]

58 **Manwani R**, Page J, Lane T, Burniston M, Skillen A, Lachmann HJ, Gillmore JD, Fontana M, Whelan C, Hawkins PN, Wagner T, Wechalekar AD. A pilot study demonstrating cardiac uptake with 18F-florbetapir PET in AL amyloidosis patients with cardiac involvement. *Amyloid* 2018; **25**: 247-252 [PMID: 30661419 DOI: 10.1080/13506129.2018.1552852]

59 **Law WP**, Wang WY, Moore PT, Mollee PN, Ng AC. Cardiac Amyloid Imaging with 18F-Florbetaben PET: A Pilot Study. *J Nucl Med* 2016; **57**: 1733-1739 [PMID: 27307344 DOI: 10.2967/jnumed.115.169870]

60 **Lee SP**, Suh HY, Park S, Oh S, Kwak SG, Kim HM, Koh Y, Park JB, Kim HK, Cho HJ, Kim YJ, Kim I, Yoon SS, Seo JW, Paeng JC, Sohn DW. Pittsburgh B Compound Positron Emission Tomography in Patients With AL Cardiac Amyloidosis. *J Am Coll Cardiol* 2020; **75**: 380-390 [PMID: 32000949 DOI: 10.1016/j.jacc.2019.11.037]

61 **Dorbala S**, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA, Fontana M, Gheysens O, Gillmore JD, Glaudemans AWJM, Hanna MA, Hazenberg BPC, Kristen AV, Kwong RY, Maurer MS, Merlini G, Miller EJ, Moon JC, Murthy VL, Quarta CC, Rapezzi C, Ruberg FL, Shah SJ, Slart RHJA, Verberne HJ, Bourque JM. 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**: 659-673 [PMID: 31468377 DOI: 10.1007/s12350-019-01761-5]

62 **Lang RM**, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; **28**: 1-39.e14 [PMID: 25559473 DOI: 10.1016/j.echo.2014.10.003]

63 **Tilkemeier PL**, Bourque J, Doukky R, Sanghani R, Weinberg RL. ASNC imaging guidelines for nuclear cardiology procedures : Standardized reporting of nuclear cardiology procedures. *J Nucl Cardiol* 2017; **24**: 2064-2128 [PMID: 28916938 DOI: 10.1007/s12350-017-1057-y]

64 **Falk RH**, Alexander KM, Liao R, Dorbala S. AL (Light-Chain) Cardiac Amyloidosis: A Review of Diagnosis and Therapy. *J Am Coll Cardiol* 2016; **68**: 1323-1341 [PMID: 27634125 DOI: 10.1016/j.jacc.2016.06.053]

65 **Maurer MS**, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C; ATTR-ACT Study Investigators. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *N Engl J Med* 2018; **379**: 1007-1016 [PMID: 30145929 DOI: 10.1056/NEJMoa1805689]

66 **Benson MD**, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, Planté-Bordeneuve V, Barroso FA, Merlini G, Obici L, Scheinberg M, Brannagan TH, Litchy WJ, Whelan C, Drachman BM, Adams D, Heitner SB, Conceição I, Schmidt HH, Vita G, Campistol JM, Gamez J, Gorevic PD, Gane E, Shah AM, Solomon SD, Monia BP, Hughes SG, Kwoh TJ, McEvoy BW, Jung SW, Baker BF, Ackermann EJ, Gertz MA, Coelho T. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. *N Engl J Med* 2018; **379**: 22-31 [PMID: 29972757 DOI: 10.1056/NEJMoa1716793]

67 **Adams D**, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, Tournev I, Schmidt HH, Coelho T, Berk JL, Lin KP, Vita G, Attarian S, Planté-Bordeneuve V, Mezei MM, Campistol JM, Buades J, Brannagan TH, Kim BJ, Oh J, Parman Y, Sekijima Y, Hawkins PN, Solomon SD, Polydefkis M, Dyck PJ, Gandhi PJ, Goyal S, Chen J, Strahs AL, Nochur SV, Sweetser MT, Garg PP, Vaishnaw AK, Gollob JA, Suhr OB. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. *N Engl J Med* 2018; **379**: 11-21 [PMID: 29972753 DOI: 10.1056/NEJMoa1716153]