Imaging in Cardiac Amyloidosis

Imágenes en la amiloidosis cardíaca

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ABSTRACT

Cardiac amyloidosis is a systemic disorder caused by the extracellular deposition of fibrils of insoluble proteins that misfold and deposit in the myocardium. Patients with amyloidosis and cardiac involvement have higher mortality rate than those without cardiac involvement. The two most prevalent types are amyloidosis with cardiac involvement are light-chain amyloidosis (AL) due to immunoglobulin light chain deposition and transthyretin amyloidosis (ATTR) due to deposition of mutated or senile forms of the transthyretin (TTR) protein. The aim of this paper is to review the different modalities of cardiac imaging tests (echocardiography, cardiac magnetic resonance imaging, nuclear medicine images and computed tomography scan) that can determine the severity of cardiac involvement in patients with amyloidosis, the type of amyloidosis and its prognosis. Finally, a diagnostic algorithm is proposed to determine cardiac involvement in amyloidosis, tailored to the diagnostic tools locally available with a practical and clinical approach.

Key words: Amyloidosis / diagnostic imaging - Cardiomyopathies / diagnostic imaging - Echocardiography - Magnetic Resonance Imaging

RESUMEN

La amiloidosis es un desorden sistémico producido por el depósito de fibrillas de proteínas insolubles que se pliegan y depositan en el miocardio. Los pacientes con amiloidosis y compromiso cardiaco tienen mayor mortalidad respecto a pacientes sin compromiso cardiaco. Las dos formas de amiloidosis más prevalentes que se asocian con compromiso cardiaco son la amiloidosis AL, por el depósito de las cadenas livianas de las inmunoglobulinas, y la amiloidosis ATTR, por el depósito de la proteína transtiretina (TTR) en forma mutada o senil. Este artículo tiene el objetivo de revisar las diferentes modalidades de imágenes cardiacas (ecocardiografía, resonancia magnética cardiaca, medicina nuclear y tomografía) que permiten determinar la severidad del compromiso cardíaco en pacientes con amiloidosis, el tipo de amiloidosis y su pronóstico. Finalmente, se sugiere un algoritmo diagnóstico para determinar el compromiso cardíaco en la amiloidosis adaptado a las herramientas diagnósticas disponibles localmente, con un enfoque práctico y clínico.

Palabras clave: Amiloidosis/diagnóstico por imágenes - Cardiomiopatías/diagnóstico por imágenes - Ecocardiografía - Imagen por Resonancia Magnética

INTRODUCTION

Cardiac amyloidosis is a systemic disorder caused by the extracellular deposition of fibrils of insoluble proteins that misfold and deposit in the myocardium. (1, 2) Patients with amyloidosis and cardiac involvement have higher mortality compared with those without cardiac involvement. (2, 3) More than 30 proteins can cause amyloidosis, the two most prevalent types being light-chain amyloidosis (AL) due to immunoglobulin light chain deposition and transthyretin amyloidosis (ATTR) due to deposition of mutated or senile forms of the transthyretin (TTR) protein. The aim of this paper is to review the different cardiac imaging tests (echocardiography, cardiac magnetic resonance imaging, nuclear medicine images and computed tomography scan) that can determine the severity of cardiac

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involvement in patients with amyloidosis, the type of amyloidosis and its prognosis.

Echocardiography

Echocardiography is usually the method of choice for the initial evaluation of cardiac involvement due to its wide availability, noninvasive nature, optimal spatial and temporal resolution, and low cost. There are different signs suggestive of cardiac amyloidosis (CA), which are neither confirmatory nor specific, especially in the initial stage of the disease. (4-7) The presence of ventricular wall thickening is suggestive of CA in the absence of valvular abnormalities or hypertension, or when the magnitude is inappropriate with respect to ECG voltages. (5) Ventricular wall thickening associated with low ECG voltages is characteristic of CA. (8, 9)

Phelan et al. compared the echocardiographic parameters in ATTR and AL (n: 172) and found that patients with wild type ATTR (wtATTR) had greater left ventricular wall thickness and similar involvement of systolic longitudinal strain than those with AL though associated with lower mortality. (10) This suggests that an additional mechanism besides amyloid infiltration, such as direct toxicity of light chains, affects the myocardium in AL.

Left ventricular hypertrophy (LVH) is typically concentric and symmetric, but an asymmetric pattern is present in up to 23% of patients with wtATTR. (11) The presence of an obstructive pressure gradient is unusual and, in the experience of the Mayo Clinic, 0.9% of patients undergoing myectomy were found to have amyloidosis. (12)

Early cardiac involvement is associated with grade I diastolic dysfunction that progresses to typical restrictive cardiomyopathy in advanced disease. (13)

Amyloidosis usually presents with preserved left ventricular ejection fraction (LVEF), but systolic dysfunction may develop in advanced stages. Coronary involvement due to macrovascular or microvascular disease can cause regional wall motion abnormalities. (14) Reduced LVEF is more common in hereditary ATTR (hATTR) with Val122Ile genotype abnormality compared with wtATTR, indicating a more advanced stage of the disease upon diagnosis and reduced survival. (15)

Both chamber function and myocardial fiber function are affected (Figure 1). (16-18) The prevalence of two-dimensional longitudinal strain abnormalities in CA ranges from 93% to 100%, even with preserved systolic function. (19) In any type of CA, systolic deformation (measured by longitudinal strain) is preserved in the apical segments and is significantly reduced in absolute values in the mid and basal segments. This apical sparing pattern improves the specificity in the diagnosis. (10, 20) A ratio of apical longitudinal strain/mid strain + basal longitudinal strain >1 could differentiate CA from hypertrophic cardiomyopathy (sensitivity 93%, specificity 82% and area under the ROC curve 0.91) and from aortic stenosis (sensitivity 93%, specificity 82% and area under the ROC curve 0.97). (22) This finding was also confirmed in Fabry disease and Friedrich ataxia (Figure 1). In this sense, a cut-off point >4.1 in the relationship between LVEF and systolic longitudinal strain presented better performance in the differential diagnosis with other forms of hypertrophy (sensitivity 90%, specificity 92% and area under the ROC curve 0.9). (23) Furthermore, in AL patients, mean longitudinal ventricular strain is a strong predictor of clinical outcome, superior to Doppler echocardiography measurements. (21)
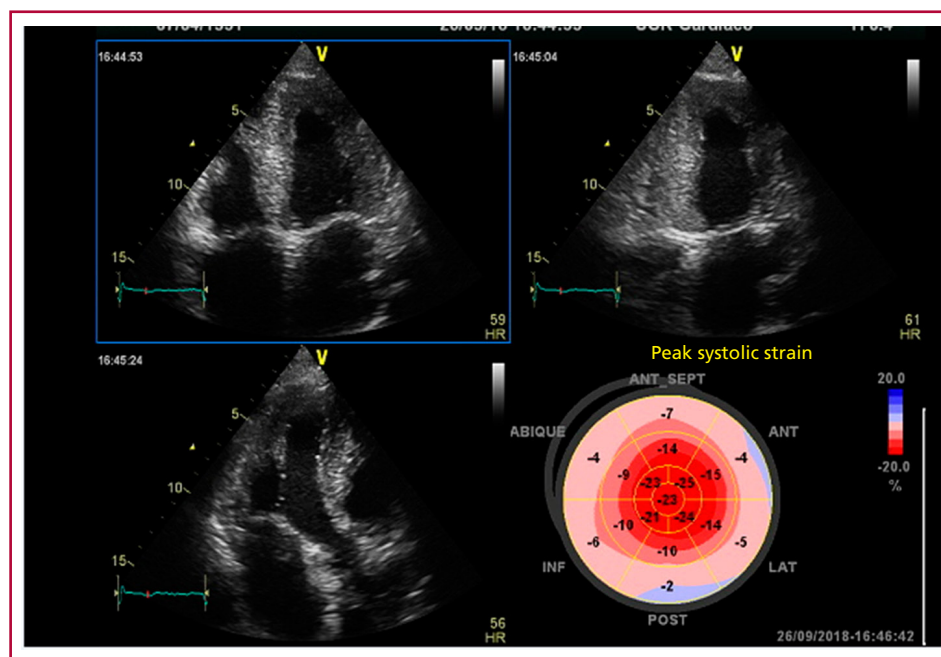

Fig. 1. Echocardiography with strain measurement by speckle-tracking. The image shows concentric and symmetric hypertrophy of left heart chambers, biatrial dilation and the typical plot of systolic longitudinal strain ("Japanese flag") with reduced deformation of the basal and mid-ventricular segments and apical sparing.

Other echocardiographic signs associated with CA are right ventricular hypertrophy and dysfunction, tricuspid annulus peak systolic excursion <14 mm or reduced deformation of the right ventricular basal segment. (24-27) Mild pericardial effusion occurs in 40 to 60% of the cases. (28, 29) In patients undergoing percutaneous transcatheter aortic valve replacement (TAVR) for aortic stenosis, the presence of an average tissue Doppler mitral annular S' <6 cm/s had 100% sensitivity to predict a positive cardiac scintigraphy scan. (30)

Up to 90% of patients with AL have cardiac involvement, and of these approximately 50% have diastolic heart failure with clinical signs of right heart failure at the time of diagnosis. (31) The absence of a restrictive pattern does not rule out infiltrative involvement, and not every restrictive pattern is secondary to CA. (32-35) Moreover, it is usual to find amyloid infiltration of the atrial wall with dilation of both atria (36, 37) and increased atrial septal thickness in 60% of cases, (38) and reduction of left atrial strain indicates advanced atrial involvement (39-42).

Recommendations for echocardiography
- Doppler-echocardiography with evaluation of longitudinal strain in patients with suspected CA.
- The different echocardiographic parameters suggestive of CA do not confirm the diagnosis or the subtype of amyloidosis.
- In the presence of systemic amyloidosis diagnosed by biopsy of non-cardiac tissue, the characteristic findings on echocardiography or cardiac magnetic resonance imaging, combined with clinical parameters and serum biomarkers may be sufficient to

define cardiovascular involvement.
- The analysis of longitudinal strain is useful to monitor patients with CA. It is suggested to repeat it at an interval of 6 months or greater, or in the presence of clinical worsening.

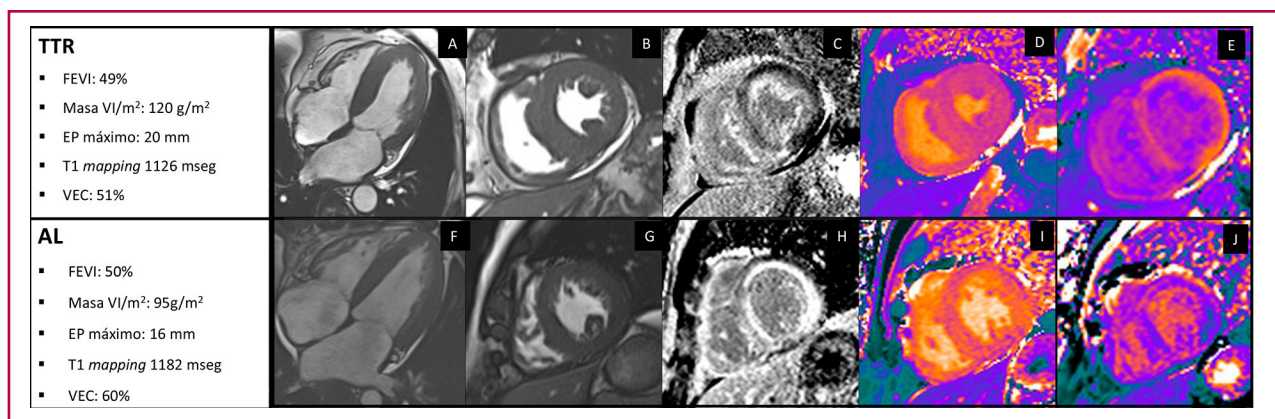**Cardiac magnetic resonance imaging**
Cardiac magnetic resonance imaging (CMRI) provides high-definition images for structural evaluation, with high spatial resolution and reproducibility, and, additionally, it can assess tissue characterization (Figure 2).

Cine imaging
Cine imaging can evaluate end-diastolic and end-systolic volumes, stroke volume, wall thickness and LVEF, constituting the gold-standard for the evaluation of these parameters. (43) In patients with poor ultrasound window, CMRI is an alternative for the diagnosis of amyloidosis and is commonly used in AL amyloidosis when there are doubts about LVEF, which is an important predictor of prognosis.

Late gadolinium enhancement
Late gadolinium enhancement (LGE) is most relevant for the diagnosis of CA. The characteristic pattern is diffuse subendocardial or transmural LGE involving the left ventricle with null signal of blood pool. This LGE pattern is very accurate for the diagnosis of amyloidosis (sensitivity 86% and specificity 92%). (44) There may be atypical presentations with focal intramyocardial enhancement that may correspond to incipient forms. (45) Extensive myocardial involvement with transmural LGE and increased wall

TTR
- FEVI: 49%
- Masa VI/m²: 120 g/m²
- EP máximo: 20 mm
- T1 *mapping* 1126 mseg
- VEC: 51%

AL
- FEVI: 50%
- Masa VI/m²: 95g/m²
- EP máximo: 16 mm
- T1 *mapping* 1182 mseg
- VEC: 60%

WT: wall thickness; LVEF: left ventricular ejection fraction; ECV: extracellular volume; LV: left ventricle.

Fig. 2. Cardiac magnetic resonance imaging in patients with ATTR and AL. *Upper row*: Patient with ATTR. *Lower row*: Patient with AL. Both patients were male, with similar involvement of systolic ventricular function. TTR amyloidosis had higher ventricular mass and greater wall thickness than AL. ECV was somewhat greater in AL. T1 mapping was similar in both patients. *Upper row*: A and B) cine magnetic resonance imaging in four-chamber view and mid-ventricular short axis view; C) late gadolinium enhancement in the subendocardium; D) native T1 mapping; E) T1 mapping after gadolinium administration. *Lower row*: F and G) cine magnetic resonance imaging in four-chamber view and mid-ventricular short axis view; H) late gadolinium enhancement in the subendocardium; I) native T1 mapping; J) T1 mapping after gadolinium administration

thickness may suggest ATTR. (46) However, the differentiation between ATTR and AL is not clear. The correct time for obtaining LGE images is short, 4 to 5 min after gadolinium injection. If myocardial tissue crosses the null point at an earlier or at the same inversion time as blood, it indicates increased gadolinium retention in the myocardium. (47) Phase-sensitive inversion recovery (PSIR) LGE acquisition provides appropriate images with automatic nulling (48, 49).

The quantification of LGE is not standardized (49) and the administration of gadolinium may not be recommended in patients with kidney dysfunction. Both limitations can be managed with T1 mapping.

T1 mapping and extracellular volume quantification

The T1 mapping technique is a pixel-by-pixel method of quantifying T1 relaxation time to characterize the myocardial tissue without contrast enhancement. (50) Native T1 (nonenhanced) signal is prolonged in the myocardium with deposition of amyloid material and is specific for the diagnosis of CA. (49) T1 values >1060 ms using 1,5 Tesla scanners can identify patients with CA. (48-54) However, T1 cutoff values for 1.5 or 3.0 Tesla scanners and for equipments from different manufacturers require better standardization.

Myocardial extracellular volume (ECV) can be estimated by measuring T1 relaxation time, before and after the administration of gadolinium. Normal ECV is <25% of the myocardial mass. (49) The ECV is a standardized measurement independent of the magnet field of the equipment (e.g., 1.5 or 3.0 Tesla), brand and dose of gadolinium administered. Elevated ECV is associated with adverse outcome in patients with CA and would be a better predictor of adverse events than native T1 mapping. (50-52) Finally, the quantification of ECV, by accurately measuring the extent of amyloid infiltration, may be useful in assessing the response to treatment. (51)

Recommendations for CMRI

- Alternative for the diagnosis of patients with poor ultrasound window and suspected amyloidosis.
- Confirms CA in patients with wall thickening, subendocardial enhancement and nulled blood pool.
- Cardiac MRI findings cannot differentiate AL from ATTR.
- ECV evaluated by CMRI could be useful to assess response to treatment.

Cardiac scintigraphy with phosphonates

Several studies have demonstrated that scintigraphy with phosphonates labeled with 99mTc has high sensitivity and specificity for the diagnosis of ATTR. (55, 56) Differentiating the subtype of amyloidosis is crucial to guide diagnosis, prognosis and treatment. (57) Scintigraphy with phosphonates provides an accurate diagnosis of TTR cardiomyopathy in patients without monoclonal protein deposition, thus avoiding endomyocardial biopsy in most cases (sensitivity 92.2% and specificity 95.4%). (58, 59)

Pyrophosphate (PYP), hydroxymethylene diphosphonate (HMDP) and 3-diphosphono-1,2-propanedicarboxylic acid (DPD) labeled with ^{99m}Tc are recommended by the international guidelines; ^{99m}Tc-PYP and ^{99m}Tc-HMDP are used in our country. (60-62) ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) is not recommended due to its low diagnostic sensitivity. (55, 56) Endomyocardial biopsies of patients with ATTR had greater density of microcalcifications, supporting the hypothesis of a calcium-mediated mechanism of these tracers binding to amyloid fibrils in ATTR. (63, 64)

Scintigraphy protocols include planar imaging followed by single photon emission computed tomography (SPECT) imaging to visualize myocardial uptake. (55, 60, 61) The recommended timing of image acquisition after injection of the radiotracer varies from 1 to 3 hours. (65, 66) Scintigraphy with phosphonates is a relatively simple test and can be used in patients with atrial fibrillation, implantable devices, kidney failure and allergy to contrast agents. (56)

Imaging interpretation

Quantification of myocardial uptake (67-69)

1. Semiquantitative analysis: Visual comparison with bone uptake (ribs) at 3 h, described by Perugini et al. (67) (Figure 3 and Table 1)
A visual score ≥2 in planar or SPECT images is considered positive for ATTR and <2 is considered negative.
2. Quantitative analysis: Heart-to-contralateral lung uptake ratio (H/CL ratio)
   a. 1 h after injection of 99mTc-PYP described by Bokhari et al.: (68) a H/CL ratio ≥1.5 on 1 h images is classified as positive for ATTR, while a H/CL ratio <1.5 is considered negative.
   b. 3 h: The validated cutoff value is ≥1.3 (Figure 4).

Myocardial uptake of phosphonates is not always due to ATTR: AL, myocardial infarction (acute/subacute), hydroxychloroquine toxicity and rare forms of amyloidosis can cause false positive results. In equivocal studies due to blood pool uptake, rib fractures or
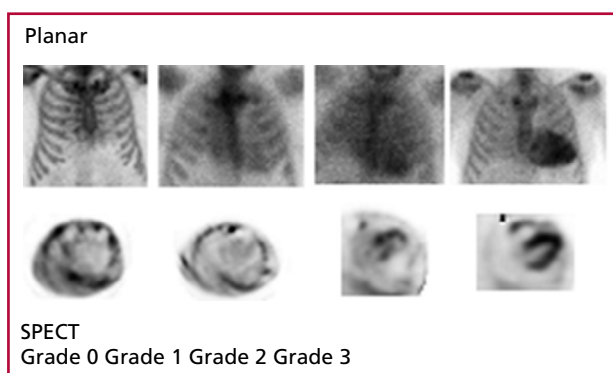

Planar

SPECT
Grade 0 Grade 1 Grade 2 Grade 3

Fig. 3. Semiquantitative analysis of 99mTc-HMDP uptake: planar and SPECT imaging

Table 1. Semiquantitative analysis Visual grading system of ^{99m}Tc (-PYP, -DPD, -HMDP) myocardial uptake compared with bone uptake

OR (95% CI)	
Grade 0	No myocardial uptake and normal rib uptake
Grade 1	Myocardial uptake < rib uptake
Grade 2	Myocardial uptake equal to rib uptake
Grade 3	Myocardial uptake > rib uptake (with mild or absent rib uptake)

Fig. 4. Quantitative analysis: Example of ^{99m}Tc-PYP cardiac uptake quantification based on heart-to-contralateral lung uptake ratio (H/CL ratio)
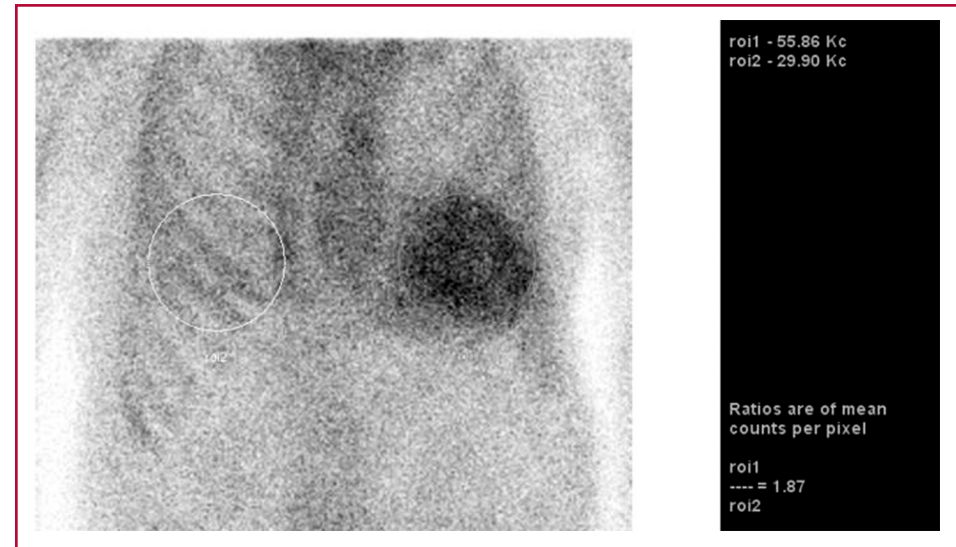
degenerative bone disease, low dose computed tomography imaging fused with SPECT can identify these factors. Cardiac scintigraphy should be interpreted in the context of a global evaluation of the patient. (65, 66)

Recommendations and most common indications of scintigraphy with phosphonates for cardiac amyloidosis

- Unexplained heart failure and increased left ventricular wall thickness (> 12 mm).
- Heart failure of unknown etiology with preserved left ventricular ejection fraction in patients >60 years of age.
- Patients (especially elderly men) with neuropathy, bilateral carpal tunnel syndrome, low-flow, low-gradient aortic stenosis, or atrial arrhythmias of unexplained cause with signs/symptoms of heart failure.
- Diagnosis of ATTR in persons with CMRI or echocardiography suggestive of CA.
- Cardiac evaluation of patients with known hereditary amyloidosis.
- Scintigraphy is not indicated to monitor treatment of cardiac ATTR.

Multidetector computed tomography scan

Cardiac multidetector computed tomography (MDCT) scan provides accurate evaluation of volumes, systolic function, wall thickness and ventricular mass. The prevalence of wtATTR is high in elderly patients evaluated for TAVR (14% to 16%) and can be sus-

pected by the presence of a disproportionate increase in ventricular mass on MDCT images. (70-75) There are new developments in MDCT based on the kinetics of iodinated contrast material to measure ECV in a similar way to CMRI with gadolinium. (76-79) Normal ECV measured by MDCT is 27%. Values >31% have demonstrated sensitivity of 94% and specificity of 48% for the diagnosis of CA. (76-81)

Integration of imaging tests and conclusions

In this paper, we have reviewed the different modalities of cardiac imaging tests to determine the severity of cardiac involvement in patients with amyloidosis. The challenge for the physician who suspects or evaluates a patient with amyloidosis is to rationally integrate the different imaging findings to establish cardiac involvement and its etiology. A diagnostic algorithm is proposed, highlighting the fundamental role of echocardiography when amyloidosis is suspected in the initial evaluation of patients (Figure 5). The presence of the following echocardiographic findings suggests amyloidosis:

a) Increased ventricular wall thickness without a clear cause with reduced longitudinal systolic strain (apical sparing).

b) Discordance between ventricular wall thickness and ECG voltages.

c) Heart failure with preserved LVEF with signs of systemic venous congestion and restrictive phenotype.

d) Increased biventricular wall thickness.

e) Low-flow, low gradient aortic stenosis.

In any of the clinical contexts, the presence of natriuretic peptide levels disproportionately elevated for the degree of the clinical findings, persistently elevated troponin levels in the absence of acute coronary syndrome, a history of carpal tunnel syndrome, lumbar spinal stenosis or spontaneous rupture of the biceps' tendon, a diagnosis of myeloma or monoclonal gammopathy, and family history of cardiomyopathy provide information. (43)

In many cases, the diagnosis of amyloidosis is suspected based on CMRI ordered in the initial evaluation of cardiomyopathies. Late gadolinium enhancement with diffuse subendocardial pattern and diffuse increased wall thickness are strongly suggestive of amyloidosis. Cardiac scintigraphy is essential to differentiate AL from ATTR. The diagnosis of familiar ATTR requires genetic tests. If echocardiography or CMRI are highly suggestive of amyloidosis and the scintigraphy is negative or equivocal, further evaluation, as endomyocardial biopsy, should be considered.
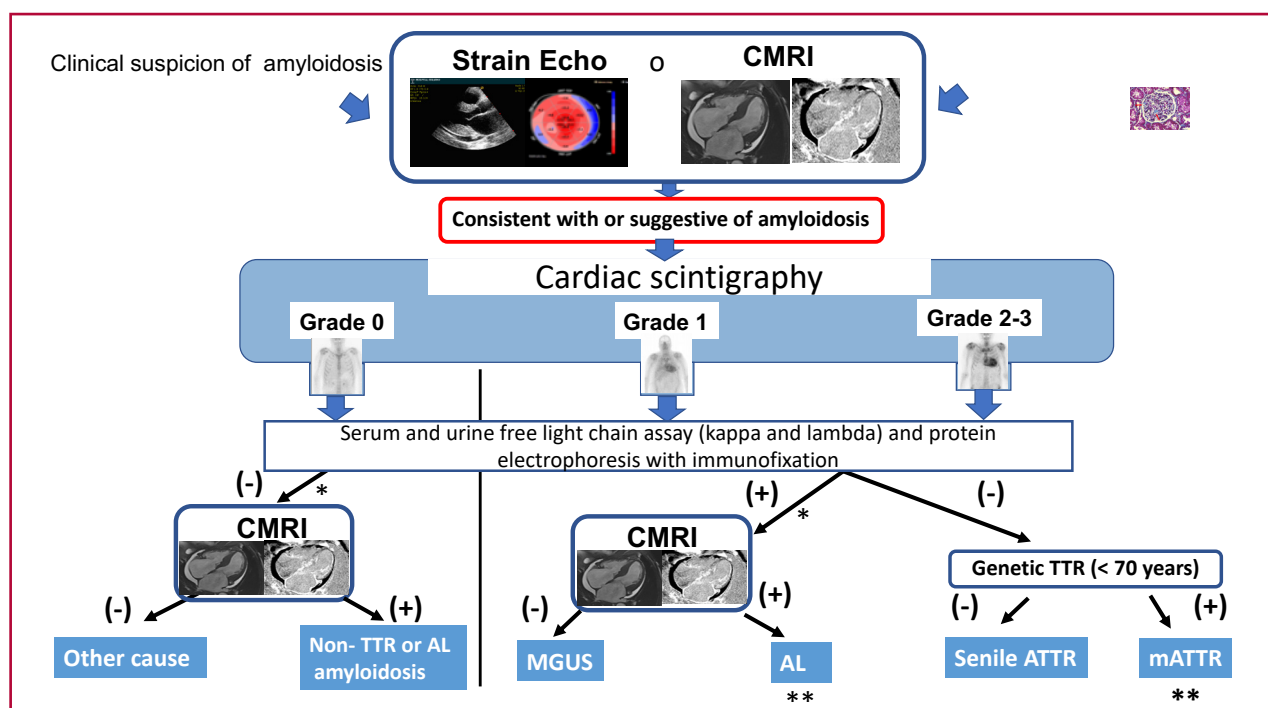
*Review or order CMRI with gadolinium-based contrast agent and mapping techniques
**CMRI with mapping, the estimation of extracellular volume may quantify the severity of myocardial infiltration during follow-up

Clinical suspicion

- Heart failure with preserved ventricular function
- Low gradient aortic stenosis
- History of carpal tunnel syndrome or spinal stenosis
- Intolerance to beta blockers or antihypertensive drugs
- Blood pressure normalization in hypertensive patients
- Kidney failure / nephrotic syndrome
- ECG with low QRS voltage or abnormal Q waves
- Macroglossia / periorbital bruising
- Small fiber neuropathy
- Orthostatic hypotension
- Left ventricular hypertrophy / RV or valvular thickening
- Diagnosis of hypertrophic cardiomyopathy in the elderly
- Family history of ATTR
- Marked elevation of pro-BNP and troponin

Diagnostic criteria

- Diagnosis of ATTR: at least positive scintigraphy and an echocardiogram or CMRI consistent with amyloidosis. In general, biopsy is not necessary for the diagnosis.
- mATTR requires confirmation by genetic test of a known mutation or consistent family history
- The diagnosis of AL requires tissue biopsy confirmation (e.g., abdominal fat, gums, extracardiac organ), monoclonal light-chains and typical evidence of cardiac involvement with at least two imaging techniques.
- Cardiac involvement due to amyloidosis: requires at least two imaging techniques (echocardiogram, CMRI or scintigraphy) with an abnormal finding characteristic of amyloidosis.
- AL requires confirmation by immunohistochemistry.
- Grade 0 scintigraphy indicates very low probability of ATTR.

Fig. 5. Diagnostic algorithm of imaging tests in amyloidosis AL: light-chain amyloidosis; Echo strain: echocardiogram with strain measurement; MGUS: monoclonal gammopathy of uncertain significance; CMRI: cardiac magnetic resonance imaging, wall thickness; TTR: transthyretin; ATTR: transthyretin amyloidosis; mATTR: mutant transthyretin amyloidosis

The diagnostic criteria for the combination of imaging tests in different clinical scenarios are summarized in Figure 5.

Clinical suspicion, rational evaluation, and integration of other parameters as biomarkers, free light chains, electrophoretic proteinogram and imaging tests are the keys to the diagnosis and to define the extent of cardiac involvement and the type of amyloidosis. Once the disease has been defined, the prognosis and the different therapeutic modalities can be established.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

REFERENCES

1. Kittleson MM, Maurer MS, Ambardekar AV, Bullock-Palmer RP, Chang PP, Eisen HJ, et al. Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement From the American Heart Association. American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. Circulation 2020;142:e7-e22. https://doi.org/10.1161/CIR.0000000000000792
2. Palladini G, Barassi A, Klersy C, Pacciolla R, Milani P, Sarais G, et al. The combination of high-sensitivity cardiac troponin T (hs-cTnT) at presentation and changes in N-terminal natriuretic peptide type B (NT-proBNP) after chemotherapy best predicts survival in AL amyloidosis. Blood 2010;116:3426-30. https://doi.org/10.1182/blood-2010-05-286567
3. Maurer M, Elliott P, Comenzo R, Semigran M, Rapezzi C. Addressing Common Questions Encountered in the Diagnosis and Management of Cardiac Amyloidosis. Circulation 2017;135:1357-77. https://doi.org/10.1161/CIRCULATIONAHA.116.024438
4. Jurcuţ R, Onciul S, Adam R, Stan C, Coriu D, Rapezzi C, et al. Multimodality imaging in cardiac amyloidosis: a primer for cardiologists. Eur Heart J Cardiovasc Imaging 2020;21:833-44. https://doi.org/10.1093/ehjci/jeaa063
5. García-Pavía P, Tomé-Esteban MT, Rapezzi C. Amyloidosis. Also a heart disease. Rev Esp Cardiol 2011; 64:797-808. https://doi.org/10.1016/j.recesp.2011.05.003
6. Dorbala S, Cuddy S, Falk RH. How to Image Cardiac Amyloidosis: A Practical Approach. JACC Cardiovasc Imaging 2020;13:1368-83. doi:10.1016/j.jcmg.2019.07.015. https://doi.org/10.1016/j.jcmg.2019.07.015
7. González-López E, López-Sáinz Á, García-Pavia P. Diagnosis and treatment of transthyretin cardiac amyloidosis. progress and hope. Rev Esp Cardiol 2017;70: 991-1004. https://doi.org/10.1016/j.recesp.2017.05.018
8. Carroll J, Gaasch W, McAdam K. Amyloid cardiomyopathy: characterization by a distinctive voltage/mass relation. Am J Cardiol 1982;49:9-13. https://doi.org/10.1016/0002-9149(82)90270-3
9. González-López E, Gagliardi C, Domínguez F, Quarta CC, de Haro-Del Moral FJ, Milandri A, et al. Clinical characteristics of wild-type transthyretin cardiac amyloidosis:disproving myths. Eur Heart J 2017;38:1895-904. https://doi.org/10.1093/eurheartj/ehx043
10. Phelan D, Thavendiranathan P, Popovic Z, Collier P, Griffin B, Thomas JD, et al. Application of a parametric display of two-dimensional speckle-tracking longitudinal strain to improve the etiologic diagnosis of mild to moderate left ventricular hypertrophy. J Am Soc Echocardiogr 2014; 27:888-95. https://doi.org/10.1016/j.echo.2014.04.015
11. González-López E, Gagliardi C, Domínguez F, Quarta CC, de Haro-Del Moral FJ, et al. Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths. Eur Heart J 2017; 38:1895-904. https://doi.org/10.1093/eurheartj/ehx043
12. Helder MR, Schaff HV, Nishimura RA, Gersh BJ, Dearani JA, Ommen SR, et al. Impact of incidental amyloidosis on the prognosis of patients with hypertrophic cardiomyopathy undergoing septal myectomy for left ventricular outflow tract obstruction. Am J Cardiol 2014;114:1396-9. https://doi.org/10.1016/j.amjcard.2014.07.058
13. Grogan M, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, et al. Natural History of Wild-Type Transthyretin cardiac amyloidosis and risk stratification using a novel staging system. J Am Coll Cardiol 2016;68:1014-20.https://doi.org/10.1016/j.jacc.2016.06.033
14. Dubrey SW, Cha K, Skinner M, LaValley M, Falk RH. Familial and primary (AL) cardiac amyloidosis: echocardiographically similar diseases with distinctly different clinical outcomes. Heart 1997;78:74-82. https://doi.org/10.1136/hrt.78.1.74
15. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol 2019; 73:2872-91. https://doi.org/10.1016/j.jacc.2019.04.00
16. Cueto-García L, Reeder GS, Kyle RA, Wood DL, Seward JB, Naessens J, et al. Echocardiographic findings in systemic amyloidosis: spectrum of cardiac involvement and relation to survival. J Am Coll Cardiol 1985;6:1737-743. https://doi.org/10.1016/S0735-1097(85)80475-7
17. Habib G, Bucciarelli-Ducci C, Caforio ALP, Cardim N, Charron P, Cosyns B, et al.; EACVI Scientific Documents Committee. Multimodality imaging in restrictive cardiomyopathies: an EACVI expert consensus document in collaboration with the"Working Group on myocardial and pericardial diseases"of the European Society of Cardiology Endorsed by The Indian Academy of Echocardiography. Eur Heart J Cardiovasc Imaging 2017;18:1090-121. https://doi.org/10.1093/ehjci/jex034
18. Koyama J, Ray-Sequin PA, Davidoff R, Falk RH. Usefulness of pulsed tissue Doppler imaging for evaluating systolic and diastolic left ventricular function in patients with AL (primary) amyloidosis.Am J Cardiol 2002;89:1067-71. https://doi.org/10.1016/S0002-9149(02)02277-4
19. Quarta CC, Solomon SD, Uraizee I, Kruger J, Longhi S, Ferlito M, et al. Left ventricular structure and function in transthyretin related versus light-chain cardiac amyloidosis. Circulation 2014;129:1840-9. https://doi.org/10.1161/CIRCULATIONAHA.113.006242
20. Liu D, Hu K, Nordbeck P, Ertl G, Störk S, Weidemann F. Longitudinal strain bull's eye plot patterns in patients with cardiomyopathy and concentric left ventricular hypertrophy. Eur J Med Res 2016;21:21. https://doi.org/10.1186/s40001-016-0216-y
21. Koyam J, Falk RH. Prognostic Significance of Strain Doppler Imaging in Light-Chain Amyloidosis. J Am Coll Cardiol Img, 2010; 3:333-42. https://doi.org/10.1016/j.jcmg.2009.11.013
22. Liu D, Hu K, Niemann M, Herrmann S, Cikes M, Stork S, et al. Effect of combined systolic and diastolic functional parameter assessment for differentiation of cardiac amyloidosis from other causes of concentric left ventricular hypertrophy. Circ Cardiovasc Imaging 2013;6:1066-72. https://doi.org/10.1161/CIRCIMAGING.113.000683
23. Pagourelias ED, Mirea O, Duchenne J, Van Cleemput J, Delforge M, Bogaert J, et al. Echo parameters for differential diagnosis in cardiac amyloidosis: a head-tohead comparison of deformation and nondeformation parameters. Circ Cardiovasc Imaging 2017;10:e005588. https://doi.org/10.1161/CIRCIMAGING.116.005588
24. Bodez DT, Guellich A, Galat A, Lim P, Radu C, Guendouz Bergoend E, et al. Prognostic value of right ventricular systolic function in cardiac amyloidosis. Amyloid 2016;23:158-67. https://doi.org/10.1080/13506129.2016.1194264
25. Bellavia D, Pellikka PA, Dispenzieri A, Scott CG, Al-Zahrani GB, Grogan M, et al. 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;13:680-69. https://doi.org/10.1093/ehjci/jes009
26. Fikrle M, Paleček T, Kuchynka P, Němeček E, Bauerová L, Straub J, et al Cardiac amyloidosis: A comprehensive review. Cor et Vasa 2013; 55: e60-e75. https://doi.org/10.1016/j.crvasa.2012.11.018
27. Mohty D, Pradel S, Magne J, Fadel B, Boulogne C, Petitalot V et al. Prevalence and prognostic impact of left-sided valve thickening in systemic light-chain amyloidosis. Clin Res Cardiol 2017; 106:331-40. https://doi.org/10.1007/s00392-016-1058-x
28. González-López E, López-Sáinz Á, García-Pavia P. Diagnosis and Treatment of Transthyretin Cardiac Amyloidosis. Progress and Hope. Rev Esp Cardiol 2017;70: 991-1004. https://doi.org/10.1016/j.recesp.2017.05.018

29. Grogan M, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, Klarich KW et al. Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System. J Am Coll Cardiol 2016 6;68:1014-20. https://doi.org/10.1016/j.jacc.2016.06.033

30. Castaño A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J 2017;38:2879-87. https://doi.org/10.1093/eurheartj/ehx350

31. Falk RH, Alexander KM, Liao R, Dorbala S. AL (Light-Chain) Cardiac Amyloidosis: A Review of Diagnosis and Therapy J Am Coll Cardiol. 2016;68:1323-41. https://doi.org/10.1016/j.jacc.2016.06.053

32. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:1321-60. https://doi.org/10.1093/ehjci/jew082

33. Klein AL, Hatle LK, Taliercio CP, Oh JK, Kyle RA, Gertz MA, et al. Prognostic significance of Doppler measures of diastolic function in cardiac amyloidosis. A Doppler echocardiography study. Circulation 1991;83:808-16. https://doi.org/10.1161/01.CIR.83.3.808

34. Schiano-Lomoriello V, Galderisi M, Mele D, Esposito R, Cerciello G, Buonauro A, et al. Longitudinal strain of left ventricular basal segments and E/e0 ratio differentiate primary cardiac amyloidosis at presentation from hypertensive hypertrophy: an automated function imaging study. Echocardiography 2016;33:1335-43. https://doi.org/10.1111/echo.13278

35. Liu D, Hu K, Niemann M, Herrmann S, Cikes M, Stork S, et al. Effect of combined systolic and diastolic functional parameter assessment for differentiation of cardiac amyloidosis from other causes of concentric left ventricular hypertrophy. Circ Cardiovasc Imaging 2013;6:1066-72. https://doi.org/10.1161/CIRCIMAGING.113.000683

36. Zhao L, Tian Z, Fang Q. Risk factors and prognostic role of left atrial enlargement in patients with cardiac light-chain amyloidosis. Am J Med Sci 2016;351: 271-8. https://doi.org/10.1016/j.amjms.2015.12.015

37. Mohty D, Pibarot P, Dumesnil JG, Darodes N, Lavergne D, Echahidi N, et al. Left atrial size is an independent predictor of overall survival in patients with primary systemic amyloidosis. Arch Cardiovasc Dis 2011;104:611-8. https://doi.org/10.1016/j.acvd.2011.10.004

38. Falk RH, Plehn JF, Deering T, Schick EC Jr, Boinay P, Rubinow A. et al. Sensitivity and specificity of the echocardiographic features of cardiac amyloidosis. Am J Cardiol 1987;59:418-22. https://doi.org/10.1016/0002-9149(87)90948-9

39. Santarone M, Corrado G, Tagliagambe LM, Manzillo GF, Tadeo G, Spata M, et al. Atrial thrombosis in cardiac amyloidosis: diagnostic contribution of transesophageal echocardiography. J Am Soc Echocardiogr 1999;12:533-6. https://doi.org/10.1016/S0894-7317(99)70091-X

40. Feng D, Edwards WD, Oh JK, Chandrasekaran K, Grogan M, Martinez MW, et al. Intracardiac thrombosis and embolism in patients with cardiac amyloidosis.Circulation 2007;116:2420-6. https://doi.org/10.1161/CIRCULATIONAHA.107.697763

41. Baccouche H, Maunz M, Beck T, Gaa E, Banzhaf M, Knayer U, et al. Differentiating cardiac amyloidosis and hypertrophic cardiomyopathy by use of three-dimensional speckle tracking echocardiography. Echocardiography 2012;29:668-77. https://doi.org/10.1111/j.1540-8175.2012.01680.x

42. Mohty D, Petitalot V, Magne J, Fadel BM, Boulogne C, Rouabhia D, et al. Left atrial function in patients with light chain amyloidosis: a transthoracic 3D speckle tracking imaging study. J Cardiol 2018;71:419-27. https://doi.org/10.1016/j.jjcc.2017.10.007

43. Fine NM, Davis MK, Anderson K, Delgado DH, Giraldeau G, Kitchlu A, et al. Canadian Cardiovascular Society/Canadian Heart Failure Society Joint Position Statement on the Evaluation and Management of Patients With Cardiac Amyloidosis. Can J Cardiol 2020;36:322-34. https://doi.org/10.1016/j.cjca.2019.12.034

44. 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.https://doi.org/10.1186/s12872-016-0311-6

45. Baroni M, Nava S, Quattrocchi G, Milazzo A, Giannattasio C, Roghi A, et al. Role of cardiovascular magnetic resonance in suspected cardiac amyloidosis: late gadolinium enhancement pattern as mortality predictor. Neth Heart J 2018;26:34-40. https://doi.org/10.1007/s12471-017-1046-4

46. Dungu JN,Valencia O, Pinney JH, Gibbs S, Rowczenio D, Gilbertson JA, et al. CMR-Based Differentiation of AL and ATTR Cardiac Amyloidosis. JACC Cardiovasc Imaging 2014; 7: 132-42. https://doi.org/10.1016/j.jcmg.2013.08.015

47. White J, Kim H, Shah D, Fine N, Kim K, Wendell D, et al. CMR Imaging With Rapid Visual T1 Assessment Predicts Mortality in Patients Suspected of Cardiac Amyloidosis. JACC Cardiovasc Imaging 2014; 7: 143-56.https://doi.org/10.1016/j.jcmg.2013.09.019

48. Fontana M, Banypersad SM, Treibel TA, Maestrini V, Sado DM, White SK et al. Native T1 Mapping in Transthyretin Amyloidosis. JACC Cardiovasc Imaging 2014; 7: 157-65. https://doi.org/10.1016/j.jcmg.2013.10.008

49. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson 2017; 19: 75.https://doi.org/10.1186/s12968-017-0389-8

50. Fontana M, Banypersad SM, Treibel TA, Abdel-Gadir A, Maestrini V, Lane T, et al. Differential myocyte responses in patients with cardiac transthyretin amyloidosis and light-chain amyloidosis: a cardiac MR imaging study. Radiology 2015; 277:388-97. https://doi.org/10.1148/radiol.2015141744

51. Martínez-Naharro A, Abdel-Gadir A, Treibel TA, Zumbo G, Knight DS, Rosmini S, et al. CMR-verified regression of cardiac AL amyloid after chemotherapy. JACC Cardiovasc Imaging 2018;11:152-4.https://doi.org/10.1016/j.jcmg.2017.02.012

52. Ridouani F, Damy T, Tacher V, Derbel H, François Legou F, Isifaoui I, et al. Myocardial native T2 measurement to differentiate light chain and transthyretin cardiac amyloidosis and assess prognosis. J Cardiovasc Magn Reson 2018; 20:58. https://doi.org/10.1186/s12968-018-0478-3

53. Hundley WG, Bluemke DA, Finn JP, Flamm SD, Fogel MA, Friedrich MG, et al. ACCF/ ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the american college of cardiology foundation task force on expert consensus documents. Circulation 2010;121:2462-508. https://doi.org/10.1161/CIR.0b013e3181d44a8f

54. Baggiano A, Boldrini M, Martínez-Naharro A, Kotecha T, Petrie A, Rezk T, et al. Noncontrast Magnetic Resonance for the Diagnosis of Cardiac Amyloidosis. JACC Cardiovasc Imaging 2020; 13:69-80. https://doi.org/10.1016/j.jcmg.2019.03.026

55. Singh V FR, Di Carli MF, Kijewski M, Rapezzi, Dorbala S. State-of-the-art radionuclide imaging in cardiac transthyretin amyloidosis. J Nucl Cardiol. 2019;26:158-73. https://doi.org/10.1007/s12350-018-01552-4

56. Masri A, Bukhari S, Eisele Y, Soman P. Molecular imaging of cardiac amyloidosis. J Nucl Med 2020; 61:965-70. https://doi.org/10.2967/jnumed.120.245381

57. Siddiqi O, Ruberg F. Cardiac amyloidosis: An update on pathophysiology, diagnosis and treatment. Trends Cardiovasc Med 2018;28:10-21.https://doi.org/10.1016/j.tcm.2017.07.004

58. Guillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation 2016;133:2404-12. https://doi.org/10.1161/CIRCULATIONAHA.116.021612

59. Treglia G, Glaudemans A, Bertagna F, Hazenberg BPC, Erba PA, Giubbini R, et al. Diagnostic accuracy of bone scintigraphy in the assessment of cardiac transthyretin-related amyloidosis: a bivariate meta-analysis. Eur J Nucl Med Mol Imaging 2018;45:1945-55. https://doi.org/10.1007/s00259-018-4013-4

60. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: Part 1 of 2-Diagnostic criteria and appropriate utilization. J Nucl Cardiol 2019;26:2065-123. https://doi.org/10.1007/s12350-019-01760-6

61. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: Part 2 of 2-Diagnostic criteria and appropriate utilization. J Nucl Cardiol 2020;27:659-73.https://doi.org/10.1007/s12350-019-01761-5

62. Daquarti GJ, Meretta A, Corneli M, Costabel JP, Diez M, Masoli OH. Centellografía con fosfonatos para el diagnótico de la amiloidosis cardíaca por transitrretina. Medicina 2018;78:395-8.

63. Falk RH, Quarta CC, Dorbala S. How to image cardiac amyloidosis. Circ Cardiovasc Imaging 2014;7:553-62.https://doi.org/10.1161/CIRCIMAGING.113.001396

64. Stats MA, Stone JR. Varying levels of small microcalcifications and macrophages in ATTR and AL cardiac amyloidosis: implications for utilizing nuclear medicine studies to subtype amyloidosis. Cardiovasc Pathol 2016;25:413-7.https://doi.org/10.1016/j.carpath.2016.07.001

65. Dorbala S, Bokhari S, Miller E, Bullock-Palmer RP, Soman P, Thompson R. American Society of Nuclear Cardiology (ASNC) practice points on technetium-99m pyrophosphate imaging for transthyretin cardiac amyloidosis-1st edition in 2016, updated in 2019.

66. Dorbala S, Bokhari S, Glaudemans AW, Miller E, Bullock-Palmer R, Slart RH. et al. American Society of Nuclear Cardiology (ASNC) and European Association of Nuclear Medicine practice points on 99mTechnetium-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) and 99mTechnetium-hydroxymethylene diphosphonate (HMDP) imaging for transthyretin cardiac amyloidosis - 1st edition in 2019.

67. Perugini E, Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2- propanodicarboxylic acid scinitigraphy. J Am Coll Cardiol 2005;46:1076-84. https://doi.org/10.1016/j.jacc.2005.05.073

68. Bokhari S, Castaño A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. (99m)Tcpyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. Circ Cardiovasc Imaging 2013;6:195-201. https://doi.org/10.1161/CIRCIMAGING.112.000132

69. Campisi R, Traverso SS. Diagnosis of transthyretin cardiac amyloidosis with cadium zinc telluride cameras. Is it feasible? J Nucl Cardiol 2020;27:381-5 https://doi.org/10.1007/s12350-020-02071-x

70. De Graaf FR, Schuijf JD, Delgado V, Van Velzen JE, Kroft LJ, De Roos A, et al. Clinical application of CT coronary angiography: state of the art. Heart Lung Circ 2010 Mar;19:107-16. https://doi.org/10.1016/j.hlc.2009.11.004

71. Lin FY, Devereux RB, Roman MJ, Meng J, Jow VM, Jacobs A, et al. Cardiac Chamber Volumes, Function, and Mass as Determined by 64-Multidetector Row Computed Tomography: Mean Values Among Healthy Adults Free of Hypertension and Obesity. JACC Cardiovasc Imaging 2008;1;782-6. https://doi.org/10.1016/j.jcmg.2008.04.015

72. Henneman MM, Bax JJ, Schuijf JD, Jukema JW, Holman ER, Stokkel MP, et al. Global and regional left ventricular function: a comparison between gated SPECT, 2D echocardiography and multi-slice computed tomography. Eur J Nucl Med Mol Imaging 2006; 33:1452-60. https://doi.org/10.1007/s00259-006-0158-7

73. Treibel TA, Fontana M, Gilbertson JA, Castelletti S, White SK, Scully PR, et al. Occult transthyretin cardiac amyloid in severe calcific aortic stenosis: prevalence and prognosis in patients undergoing surgical aortic valve replacement. Circ Cardiovasc Imaging 2016;9: e005066. https://doi.org/10.1161/CIRCIMAGING.116.005066

74. Scully PR, Treibel TA, Fontana M, Lloyd G, Mullen M, Pugliese F, et al. Prevalence of cardiac amyloidosis in patients referred for transcatheter aortic valve replacement. J Am Coll Cardiol 2018; 71:463-4. https://doi.org/10.1016/j.jacc.2017.11.037

75. Castaño A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J 2017; 38:2879-87. https://doi.org/10.1093/eurheartj/ehx350

76. Scully PR, Bastarrika G, Moon JC, Treibel TA. Myocardial extracellular volume quantification by cardiovascular magnetic resonance and computed tomography. Curr Cardiol Rep 2018;20. https://doi.org/10.1007/s11886-018-0961-3

77. Sado DM, Flett AS, Banypersad SM, White SK, Maestrini V, Quarta G, et al. Cardiovascular magnetic resonance measurement of myocardial extracellular volume in health and disease. Heart 2012; 98:1436- 41. https://doi.org/10.1136/heartjnl-2012-302346

78. Treibel TA, Fontana M, Steeden JA, Nasis A, Yeung J, White SK, et al. Automatic quantification of the myocardial extracellular volume by cardiac computed tomography: synthetic ECV by CCT. J Cardiovasc Comput Tomogr 2017;11:221-6. https://doi.org/10.1016/j.jcct.2017.02.006

79. Bandula S, White SK, Flett AS, Lawrence D, Pugliese F, Ashworth MT, et al. Measurement of Myocardial Extracellular Volume Fraction by Using Equilibrium Contrast-enhanced CT: Validation against Histologic Findings. Radiology 2013;269:396-403. https://doi.org/10.1148/radiol.13130130

80. Rosmini S, Treibel TA, Bandula S, Stroud T, Fontana M, Hawkins PN, et al. Cardiac computed tomography for the detection of cardiac amyloidosis. J Cardiovasc Computed Tomograph 2017;11:155-6. https://doi.org/10.1016/j.jcct.2016.09.001

81. Bandula B, White SK, Flett AF, Lawrence D, Pugliese F, Ashworth MT, et al. Measurement of Myocardial extracellular Volume Fraction by Using equilibrium contrast-enhanced CT: Validation against Histologic Findings. Radiology 2003; 269: 396-403. https://doi.org/10.1148/radiol.13130130