Cardiovascular and Metabolic Science www.ancam.org.mx

Vol. 35 Supplement 3
October-December 2024

Mexican statement for the diagnosis and treatment of cardiac amyloidosis.

Consensus document of the Mexican Society of Cardiology, the National Association of Cardiologists of Mexico, the Mexican Association for Heart Failure, the Mexican Society of Electrophysiology and Cardiac Pacing, and the National Society of Echocardiography of Mexico

Declaración mexicana para el diagnóstico y tratamiento de la amiloidosis cardiaca.

Documento de consenso de la Sociedad Mexicana de Cardiología, la Asociación Nacional de Cardiólogos de México, la Asociación Mexicana de Insuficiencia Cardiaca, la Sociedad Mexicana de Electrofisiología y Estimulación Cardiaca y la Sociedad Nacional de Ecocardiografía de México

Enrique A Berrios-Bárcenas,[1,2] José A Cigarroa-López,[3,4,5,6] Jorge E Cossio-Aranda,[6] Zuilma Y Vásquez-Ortiz,[7,8,9] Gerardo Rodríguez-Diez,[10,11] Luis Baeza-Herrera,[12] Juan Cordero-Cabra,[13] Julieta Morales-Portano,[10] Erick Alexanderson-Rosas,[1] Isabel Carvajal-Juárez,[1,3] Amada Álvarez-Sangabriel,[1] Antonio Jordán-Ríos,[1] Juan B Ivey-Miranda,[3] Cecilia Escalante-Seyffert,[2] A Grimaldo-Flavio,[1] Pablo Hernández-Reyes,[7] José S Laínez-Zelaya,[14] Jorge A Lara-Vargas,[10] Aloha Meave-González,[1] Blanca R Ibarra-Ibarra,[1] G Koretzky-Solange,[1,15] Antonio Magaña-Serrano[3,4,5]

[1] National Institute of Cardiology Ignacio Chávez.
[2] Spanish Hospital of Mexico.
[3] Cardiology Hospital of the National Medical Center «Siglo XXI», IMSS.
[4] Mexican Association for Heart Failure.
[5] National Association of Cardiologists of Mexico.
[6] Mexican Society of Cardiology.
[7] National Institute of Nutrition Salvador Zubirán.
[8] National Society of Echocardiography of Mexico.
[9] ABC Santa Fe Medical Center.
[10] National Medical Center 20 de Noviembre, ISSSTE.
[11] Mexican Society of Electrophysiology and Cardiac Pacing.
[12] Regional Hospital of High Specialty of the Yucatan Peninsula.
[13] Puerta de Hierro Norte Hospital.
[14] Regional Hospital of High Specialty «Centenario de la Revolución Mexicana», ISSSTE.
[15] Children's Hospital of Mexico Federico Gómez.

Abbreviations:

6MW = 6-Minute Walk.
99mTc = 99mTechnetium.
99mTc-DPD = 99mTc-3, 3-diphosphono-1,2 propanedicarboxylic acid.
99mTc-HMDP = 99mTc-Hydroxymethylene diphosphonate.
99mTc-MDP = Methyl Diphosphonate.
99mTc-PYP = Pyrophosphates.
AA = Secondary Amyloidosis.
ACEI = Angiotensin-Converting Enzyme Inhibitors.
ACM = Atrial Cardiomyopathy.
AF = Atrial Fibrillation.
AH = Heavy-chain Amyloidosis.
AL = Light-chain Amyloidosis.
aPTT = activated Partial Thromboplastin Time.
ATTR = Transthyretin Amyloidosis.
ATTR-ACT = Transthyretin Amyloidosis Cardiomyopathy Clinical Trial.
ATTRwt = Senile Transthyretin Amyloidosis.
AV = Atrioventricular.
BMA = Bone Marrow Aspiration.
BNP = Brain Natriuretic Peptide.
CA = Cardiac Amyloidosis.
CHA2DS2VASc = Congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category.
CLL = Chronic Lymphocytic Leukemia.

How to cite: Berrios-Bárcenas EA, Cigarroa-López JA, Cossio-Aranda JE, Vásquez-Ortiz ZY, Rodríguez-Diez G, Baeza-Herrera L, et al. Mexican statement for the diagnosis and treatment of cardiac amyloidosis. Consensus document of the Mexican Society of Cardiology, the National Association of Cardiologists of Mexico, the Mexican Association for Heart Failure, the Mexican Society of Electrophysiology and Cardiac Pacing, and the National Society of Echocardiography of Mexico. Cardiovasc Metab Sci. 2024; 35 (s3): s263-s301. https://dx.doi.org/10.35366/118769

CM = Cardiac Magnetic Resonance Imaging.
CO = Cardiac Output.
CPET = Cardiopulmonary Exercise Testing.
CR = Cardiac Rehabilitation.
CRF = Cardiorespiratory Fitness.
BorD = Cyclophosphamide + Bortezomib + Dexamethasone.
DACs = Direct Anticoagulants.
ECG/EKG = Electrocardiogram.
ECV = Extracellular Volume.
EF = Ejection Fraction.
FDA = Food and Drug Administration.
GCW = Global Constructive Myocardial Work.
GFR = Glomerular Filtration Rate.
GLS = Global Longitudinal Strain.
GWE = Global Work Efficiency.
H/CL ratio = Heart/Contralateral Lung Ratio.
hATTR/ATTRv = Hereditary Transthyretin Amyloidosis.
HCM = Hypertrophic Cardiomyopathy.
HCT = Hematopoietic Cell Transplantation.
HF = Heart Failure.
HFpEF = Heart Failure with Preserved Ejection Fraction.
HRR = Heart Rate Reserve.
ICD = Implantable Cardioverter-Defibrillator.
IFE = Immunofixation Electrophoresis.
K/L ratio (κ/λ) = Kappa/Lambda ratio.
LA = Left Atrium.
LAFB = Left Anterior Fascicular Block.
LBBB = Left Bundle Branch Block.
LGE = Late Gadolinium Enhancement.
LV = Left Ventricle.
LVEF = Left Ventricular Ejection Fraction.
MACE = Major Adverse Cardiovascular Events.
MCF = Myocardial Contraction Fraction.
MGRS = Monoclonal Gammopathy of Renal Significance.
MGUS = Monoclonal Gammopathy of Unknown Significance.
MM = Multiple Myeloma.
MW = Myocardial Work.
NAC = National Amyloidosis Centre of the United Kingdom.
NHL = Non-Hodgkin Lymphoma.
NS = Nervous System.
NT-ProBNP = N-terminal Pro-Brain Natriuretic Peptide.
NYHA = New York Heart Association.
O2-pulse = Oxygen-pulse.
OAC = Oral Anticoagulation.
PT = Prothrombin Time.
RA = Right Atrium.
RAG = Relative Apical Gradient.
RBBB = Right Bundle Branch Block.
RELAPS = Relative Apical Gradient.
ROI = Region of Interest.
RV = Right Ventricle.
SGLT2i = Sodium-Glucose Cotransporter type 2 inhibitors.
SPECT = Single-Photon Emission Tomography.
SPECT/CT = Single-Photon Emission Tomography/Computed Tomography.
TcPYP = Phosphate Scintigraphy.
TEEs = Thromboembolic Events.
TT = Thrombin Time.
TTE/ECHO = Transthoracic Echocardiogram.
TTR = Transthyretin.
V122I = Valine 122 Isoleucine.
VE/VCO2 = Ventilatory Equivalent for Carbon Dioxide.
VKAs = Vitamin K Antagonists.
VO2 = Oxygen Uptake.
VO2peak = Peak Oxygen Uptake.
VWD = Von Willebrand Disease.

INTRODUCTION

Cardiac amyloidosis is currently emerging as a significant clinical challenge, which has led to increasing attention from the medical community due to its impact on cardiac function. This disease is characterized by the abnormal accumulation of fibrillar proteins in cardiac tissue and manifests itself as a heterogeneous entity with diverse clinical presentations and prognoses. As the understanding of amyloidosis has evolved, it is necessary to delve deeper into the generalities and specific types that affect the heart.

Due to the low sensitivity of some traditional tests to detect the presence of cardiac amyloidosis in early stages, innovative techniques in the field of imaging and biomarkers must be developed. Early identification of the disease is essential for improved prognosis.

The variability in the clinical presentation of cardiac amyloidosis and its ability to mimic other common cardiac diseases creates a diagnostic dilemma, which often leads to misdiagnoses and delays in treatment. The fact that cardiac amyloidosis sometimes acts as a great imitator raises the question of how we can improve clinical awareness and accurate differentiation between amyloidosis and other cardiac conditions to prevent redundant assessment and testing. Thus, the idea of reconsidering amyloidosis as an entity purely associated with old age also arises.

This position paper aims to evaluate and summarize the available evidence to provide health professionals with a practical and up-to-date tool based on scientific evidence, thereby seeking to improve the clinical, diagnostic and therapeutic approach to amyloidosis.

This position paper should facilitate decision-making by health professionals in daily practice. However, it does not rule out the responsibility of each professional to make appropriate and accurate decisions taking into consideration the health condition of each patient.

Class of recommendation		
I	Evidence and/or general agreement that a given procedure or treatment is effective, beneficial, useful	Is recommended/is indicated
II	Conflicting evidence and/or a divergence of opinion about the usefulness/benefit of the given procedure or treatment	
IIa	Weight of evidence/opinion is in favor of usefulness/efficacy	Should be considered
IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
III	Evidence or general agreement that the given procedure or treatment is not useful/effective, and in some cases may be harmful	Is not recommended

Levels of evidence	
A	Data derived from multiple randomized clinical trials or meta-analyses
B	Data derived from a single randomized clinical trial or large non-randomized studies
C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

PATHOPHYSIOLOGY

Amyloidosis is a disorder of protein origin that involves the extracellular deposition of amyloid fibrils, which result from the abnormal aggregation of proteins in the form of beta-pleated sheets.[1] In the cardiac context, this disruptive accumulation can compromise the structure and function of the heart, leading to a wide variety of clinical manifestations ranging from heart failure to potentially lethal arrhythmias.[2]

Cardiac amyloidosis (CA) is mainly subdivided into two main types: primary cardiac amyloidosis or AL and secondary cardiac amyloidosis or ATTR.[3] AL amyloidosis is associated with the accumulation of immunoglobulin light chains, mainly derived from abnormal plasma cells in the bone marrow.[4] On the other hand, ATTR amyloidosis originates from transthyretin, a thyroxine and retinol hormone carrier protein produced in the liver.[5]

It is essential to recognize that cardiac amyloidosis differs not only in terms of the precursor proteins involved, but also in their clinical implications and therapeutic approaches.[6] While AL amyloidosis is often associated with systemic disease and is present in the context of monoclonal gammopathy, ATTR amyloidosis may occur in a hereditary manner (hATTR) or as a senile form (ATTRwt), which primarily affects older adults.[7]

Light chain amyloidosis (AL) represents the accumulation of amyloid fibrils derived from immunoglobulin light chains that affect diverse organs, but mainly the heart, kidneys, the peripheral nervous system and the liver.[8] Transthyretin amyloidosis (ATTR) represents a complex clinical entity characterized by the accumulation of amyloid fibrils derived from the transthyretin protein that predominantly affects the heart and the peripheral nervous system.

EPIDEMIOLOGY

Cardiac amyloidosis has been considered a rare disease since, according to registries with confirmed cases, the prevalence has been estimated to be less than 5 cases per 10,000 people, which is equivalent to 0.05%.[9] However, it is possible that its prevalence is underestimated since amyloidosis is a condition whose diagnosis can go unnoticed. A recent meta-analysis showed that the prevalence could be significantly higher. For example, in autopsies in elderly subjects the frequency of amyloidosis was 21%. The prevalence of

other conditions was 7 to 12% (7% suspected hypertrophic cardiomyopathy, 7% carpal tunnel syndrome, 8% aortic stenosis, 10% heart failure with reduced or mildly reduced LVEF (left ventricular ejection fraction), and 12% heart failure with preserved LVEF).[10] It is therefore reasonable to assume that the prevalence of amyloidosis is higher than reported (0.05%). The actual statistics are still unknown.

A study published in the New England Journal of Medicine in 2020 showed that the diagnosis of amyloidosis increased (overall) by 670% over the past 30 years. AA amyloidosis (A amyloid) decreased dramatically from 13 to 3%. This is probably due to the emergence of better treatments for inflammatory diseases. In contrast, wild-type transthyretin amyloidosis (ATTRwt) increased from 3 to 14%. This is probably a reflection of the use of techniques such as Tc-pyrophosphate scintigraphy.[11]

With regard to Mexico and Latin America, the clinical and genetic characteristics of subjects with transthyretin amyloidosis were recently published by the THAOS group. In this document, data from 2,887 subjects from Mexico, Argentina and Brazil was reviewed. It was observed that the proportion of men/women was close to 50% and that the genetic variants were different between countries. In Argentina and Brazil, the most frequent variant was Val30Met, while in Mexico it was Ser50Arg. Regarding the amyloidosis phenotype (neurological, cardiac or mixed involvement), in all three countries neurological involvement was the most frequent, followed by the mixed phenotype.[12] More details were published by González-Duarte et al. in relation to Mexico, where it was observed that the 5 most frequent variants were: Ser5Arg (74%), Gly47Ala (13%), Ser52Pro (11%) and V122I/Y116H (2%). The states of Morelos and Guerrero grouped most of the cases.[13]

As previously described, the epidemiology of cardiac amyloidosis appears to be related to the diagnosed cardiac involvement. For example, regarding aortic stenosis, a meta-analysis of 1,321 subjects showed that the proportion of cardiac amyloidosis could be 11%. The risk factors for amyloidosis were old age, male gender, carpal tunnel syndrome, thicker interventricular septum, and low flow-low gradient phenotype. However, most studies considered the Tc-pyrophosphate scintigraphy as a diagnosis, which could represent an overestimation of the prevalence.[14]

In studies of patients with heart failure and preserved LVEF, a meta-analysis of 670 subjects reported that the prevalence of cardiac amyloidosis was 11%. Like aortic stenosis, male gender and greater wall thickness were risk factors for amyloidosis.[15] Finally, some epidemiological studies have focused exclusively on wild-type cardiac amyloidosis. In this regard, a meta-analysis of 2,542 subjects showed that the proportion of men included was 86.9%, suggesting that wild-type transthyretin amyloidosis primarily affects the male gender.[16]

In conclusion, one of the most important efforts worldwide to describe the epidemiology of cardiac amyloidosis is that of the THAOS investigators. This group carries out longitudinal, observational and multicenter data collection of subjects with transthyretin cardiac amyloidosis, whether inherited or wild-type. A recent report describes data from 1,069 subjects with wild-type cardiac amyloidosis and 525 subjects with hereditary cardiac amyloidosis. Among the most important findings are that biopsies are used less and less, and pyrophosphate scintigraphy is more frequent. Also, the percentage of patients diagnosed with poor functional class (NYHA III/IV) decreased from 46 to 16% in the last seven years, reflecting earlier diagnosis, which probably represents some improvements to current treatments. However, even in this era of greater knowledge about amyloidosis, the median time from symptom onset to diagnosis of cardiac amyloidosis has not changed.[17]

CLINICAL MANIFESTATIONS

The diagnosis of amyloidosis in clinical practice is difficult because the multisystem signs and symptoms reported by patients are neither sensitive nor specific to the disease. In addition, the clinical picture may go unnoticed for months or years before the final diagnosis of amyloidosis is made. This results in misdiagnoses and delays in specific medical treatment.

The symptoms and signs reported by patients are confusing, so it is not unusual for

them to have previously received alternative diagnoses due to the predominant organic involvement. Virtually any organ can be affected, except for the central nervous system. Affected organs include the following: heart (70%), kidney (60%), peripheral nervous system (15%)/autonomic (10%), gastrointestinal tract (15%), liver (20%) and soft tissues (10%).[18,19] Up to two out of three patients may have a condition that involves two or more organs, which makes diagnosis difficult. Depending on the subtype of amyloidogenic protein that is deposited in the tissues, the prevalence of organ involvement can be determined *(Table 1)*.

In order to improve the identification of the most frequent clinical manifestations of amyloidosis, we suggest dividing the organ involvement as follows *(Table 2)*.

S Amyloidosis (SA)

Secondary amyloidosis (AA) is a rare systemic complication that can develop after any chronic inflammatory disorder. The fibrils are derived from serum amyloid A (SAA) proteins, an acute phase reactant synthesized by hepatocytes under regulation of proinflammatory cytokines. In developed countries, the decrease in incidence of chronic diseases and the existence of treatments for autoimmune diseases have produced a decrease in the incidence of AA. Potentially any inflammatory disease can be complicated by AA. In developing countries, the most common cause is inflammatory arthritis.[21]

The main manifestation that occurs in 95% of patients and that determines prognosis is proteinuria, since up to 50% of patients started with nephrotic syndrome.[22] Amyloid deposits in the liver and spleen are common but of little clinical significance in the early stages of the disease, however, acute manifestations such as atraumatic organ rupture are very rare and may be more dramatic. The gastrointestinal system may also be affected, causing malabsorption, chronic diarrhea, pseudo-occlusion or bleeding.[23] Peripheral polyneuropathy and restrictive cardiomyopathy with heart failure

Table 1: Organs affected according to the type of amyloidogenic protein.

Protein	
AL amyloidosis	Heart, kidney, peripheral nervous system of autonomic and somatic branches, gastrointestinal tract, soft tissues and liver
Amyloidosis due to TTR protein deposition	Heart, kidney, liver, musculoskeletal system, eyes, soft tissues
Amyloidosis due to protein type A deposition	Kidney, spleen, liver

AL = Light chains. TTR = Transthyretin. Adapted from: Vaxman I et al.[20]

Table 2: Recommendations on symptoms and signs of cardiac amyloidosis.

Recommendation	Class of recommendation	Levels of evidence
The clinical manifestations of amyloidosis are divided into organic disorders of the following systems: cardiovascular, musculoskeletal, autonomic nervous system and somatic nervous system	I	C
In patients with clinical manifestations of CA, a diagnostic approach should be initiated	I	B

CA = Cardiac Amyloidosis.

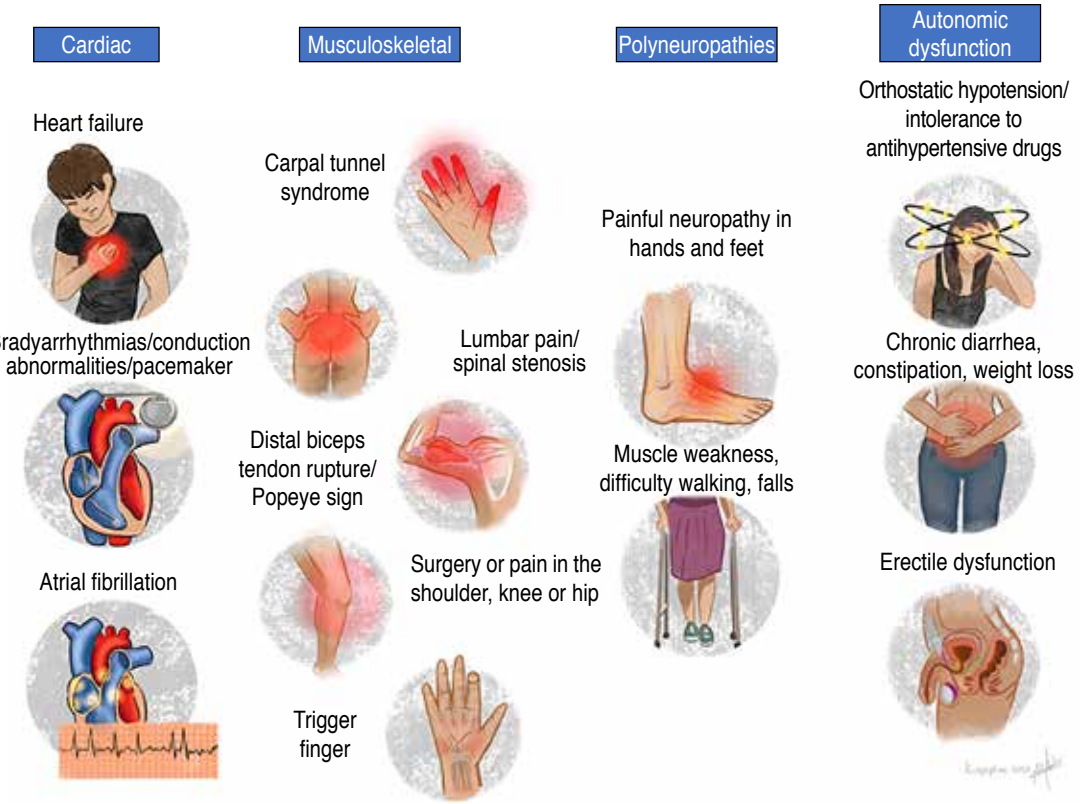

Figure 1: Clinical manifestations of patients with cardiac amyloidosis caused by transthyretin deposits. Adapted from: Kittleson M et al.[28]

are extremely rare, especially when compared with other types of amyloidosis. Pulmonary infiltrate with amyloid and thyroid enlargement have also been seen.[21]

AL Amyloidosis

The heterogeneity of the clinical presentation makes clinical suspicion difficult, which is the most important thing and will depend on the affected organ. Most of the symptoms are nonspecific and, in many cases, the diagnosis is not made at the right time, leading to an early death. Symptoms that should raise suspicion are heart failure with preserved ejection fraction, nephrotic range proteinuria, bilateral carpal tunnel syndrome, axonal peripheral neuropathy or symptoms of autonomic dysfunction. Cardiac involvement occurs in 60 to 75% of cases and generally presents with symptoms and signs of right heart failure (peripheral congestion) that include edema of the lower limbs, distension of the jugular vein, ascites and hepatic congestion, as well as dyspnea. When the conduction system is affected, patients may experience presyncope or syncope and arrhythmias and sudden death. Atypical chest pain due to small vessel disease is also common.[24]

Renal involvement is common and occurs in 50-70% of patients. It should always be suspected in a patient presenting with nephrotic syndrome with or without renal failure. Symptoms associated with AL amyloidosis and renal involvement include lower limb edema, orthostatic hypotension, foamy urine due to proteinuria, mild renal failure, and hypercholesterolemia in those patients with nephrotic syndrome. It is important to mention that nephrotic range proteinuria can occur with normal renal function.[24-26]

Macroglossia is highly suggestive of AL amyloidosis and may occur in up to 17% of patients. Other signs of infiltration include bilateral carpal tunnel syndrome, enlarged

submandibular and cervical glands, and periorbital purpura.[25,27]

Peripheral neuropathy may be indicative of NS involvement. Specific symptoms may include paresthesia, numbness, and pain in the extremities (lower symmetric sensorimotor polyneuropathy), and even muscle weakness when there is a concomitant myopathy.

Additionally, autonomic neuropathy may be present, presenting postural hypotension, erectile dysfunction, and altered gastrointestinal or bladder motility.

Specific involvement of the gastrointestinal system occurs in approximately 10% of patients and includes symptoms such as weight loss, nausea, diarrhea, altered motility, and bleeding.

Liver involvement occurs in 20% of patients and may present with hepatomegaly without apparent involvement in imaging studies or with an isolated elevation of alkaline phosphatase without increased transaminases *(Figure 1)*.[24,25]

It is important to mention that symptoms may occur simultaneously in different organs and systems, so the suspicion and integration of multisystem involvement should alert to the possibility of amyloidosis[29] *(Table 3)*.

Epidemiological studies have identified patients with associated cardiac amyloidosis in the following clinical settings: autopsy series of patients older than 85 years (25%),[30] patients with surgery for correction of carpal tunnel syndrome (10%),[31] hospitalized patients with heart failure with HFpEF (13%),[32] severe aortic stenosis (5%),[33] percutaneous aortic valve replacement (16%)[34] and spinal canal stenosis (37%).[35] Therefore, the expert group suggests the use of algorithms of clinical suspicion and diagnosis based on symptoms and organic involvement to facilitate clinical integration and initiation of diagnostic approach for amyloidosis *(Figure 2)*.

The timely and correct diagnosis of amyloidosis should be the objective of working groups involved in its care. They can be internists, cardiologists, nephrologists, hematologists or primary care physicians.

IMAGING STUDIES

Electrocardiogram (ECG)

Despite advances in imaging techniques for the diagnosis of cardiomyopathies, which emphasize the morphology, function and characterization of heart tissue, the ECG is an invaluable tool in the diagnostic work process when these conditions are suspected. In the case of cardiac amyloidosis (CA), it is important to highlight the findings described below.

Low voltage: the most peculiar data in CA is the reduction of the QRS interval voltages of (≤

Table 3: Clinical manifestations that should alert for the diagnosis of transthyretin amyloidosis.

Cardiovascular system	Somatic nervous system	Autonomic nervous system	Musculoskeletal system*
• Dyspnea • Intolerance to the administration of vasodilators and betablockers • Atrioventricular conduction disorders • Diastolic dysfunction • Persistent elevation of troponin and/or BNP/NT-ProBNP • Rapid decline (< 6 months) in 6-minute walk distance	• Muscle weakness • Frequent falls • Neuropathic pain in hands and feet «stocking glove neuropathy»	• Erectile dysfunction • Diarrhea/constipation • Orthostatic hypotension • Intolerance of anti hypertensive drugs	• Carpal tunnel syndrome • Lumbar pain due to spinal canal stenosis • Biceps tendon rupture in people over 50 years of age • Trigger fingers • History of joint replacement surgery or arthroplasty

BNP = Brain Natriuretic Peptide. NT-ProBNP = N-Terminal Pro-Brain Natriuretic Peptide. * Musculoskeletal symptoms may appear 5 to 10 years prior to the clinical diagnosis of amyloidosis. Adapted from: Nativi-Nicolau JN et al.[29]

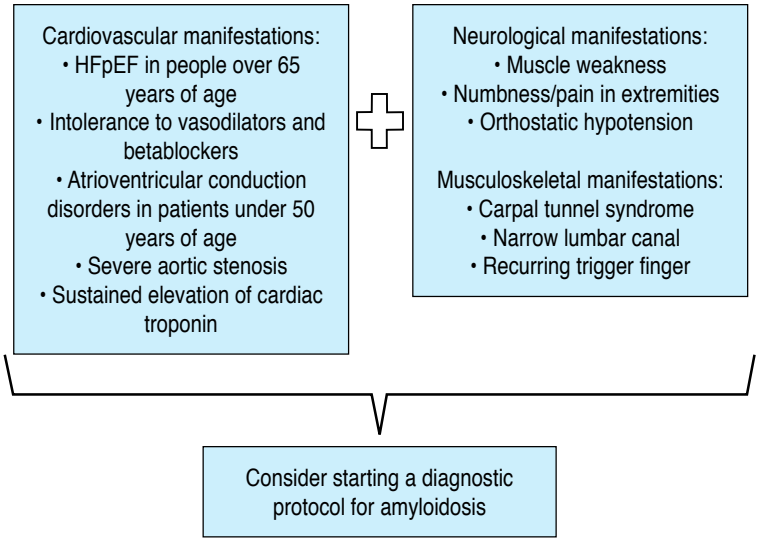

Figure 2: Proposed algorithm for the timely identification of potential patients with TTR amyloidosis.
HFpEF = Heart Failure with Preserved Ejection Fraction. Adapted from: Nativi-Nicolau JN et al.[29]

0.5 millivolts (mV) in the frontal plane leads[36,37] and sometimes accompanied by voltages of ≤ 1 mV in the precordial leads or a Sokolow/Lyon (SL) index of < 1.5 mV, disproportionate to the left ventricular (LV) thickening).[38,39] This low voltage contrast and the degree of LV thickening is due to the fact that the latter is not due to myocardial hypertrophy but to amyloid deposits in the extracellular space.[37] The prevalence of this finding is still unclear and varies depending on the studies, ranging from 25 to 90% of cases.[40,41] Some studies show a higher prevalence of transthyretin amyloidosis (ATTR), which has been reported in 50% of cases, while amyloidosis associated with light chains (AL) is reported in 30% of cases.[42,43] These studies suggest such prevalence because patients with ATTR have a progressive cardiomyopathy characterized by a slow buildup of amyloid in the myocardium, while patients with AL have acute myocarditis with early onset symptoms and rapid progression of the disease up to the final stages, with low degrees of infiltration and their condition is due to the toxic effects of light chains. Other studies[44,45] report a higher prevalence of low QRS voltage in AL (55 vs 35% in ATTR) and support this finding with the explanation that patients with ATTR usually present a higher degree of ventricular thickening due to a higher degree of infiltration (therefore, higher voltage) compared to AL.[39]

In a study of AL, the best sensitivity of 90% was reported with the combination of the low voltage criterion of (≤ 0.5 mV frontal + ≤ 1 mV precordial) and a SL index of ≤ 1.5 mV, but with a low specificity of 45%. This improves to 81% if only ≤ 0.5 mV in the frontal leads is considered, but with a decrease in sensitivity to 66%.[46] From a clinical point of view, the finding of low voltage is related to advanced stages of the disease, therefore, they present a worse prognosis, greater impairment of the functional class, high natriuretic peptides and worse right ventricular systolic function.[38,47] Other relevant findings in the evaluation of the QRS interval are that they present an abnormal axis (-30 to -90 degrees) and poor progression of the R wave in leads.[44,48] In all variants, there is a prevalence of pseudoinfarction (Q waves of ¼ the amplitude of the R or QS in 2 continuous leads)[44] that can be observed in up to 2/3 of the cases.[49]

Conduction disorders: sinus node dysfunction has been reported in AC, manifested by bradycardia and/or sinus arrest with sinus pauses[48,50] due to fibrosis and amyloid infiltration in the sinus node and its corresponding artery.[51] There may be different degrees of block at the atrioventricular level (low and high degree) with a higher prevalence in ATTRv of up to 20%.[44]

Regarding interventricular disorders, these are rare, but they do exist. They are right bundle branch block (RBBB) (more prevalent) and left bundle branch block (LBBB), which is much less frequent, and the latter only occurs with a preexisting condition.[52] The explanation, although not clear, is based on the fact that amyloid deposits affect the heart uniformly, therefore the right branch is more vulnerable. Finding disorders in both branches electrophysiologically would be unlikely since there would be no conduction in both branches. The ATTRv variant presents a higher prevalence of interventricular conduction disorders.[44] Some studies report a higher prevalence of LBBB in ATTR and of RBBB or LAFB in AL.[53]

The use of the indexed electrocardiographic criteria of Sharma et al. to diagnose cardiac amyloidosis in men with left ventricular

hypertrophy and bundle branch block, in which the sum of the total amplitude of all QRS in the 12 electrocardiogram leads is calculated, divided by the average ventricular wall thickness by TTE, can guide us to the diagnosis of CA, with a sensitivity of 100% and a specificity of 83.3% with a score less than 92.5.[54]

A relevant finding in the electrophysiological study in patients with CA is the presence of a narrow QRS with a prolonged HV interval and this is believed to be due to an infiltration of both branches and the His-Purkinje system.[55] This finding is more common in ATTR and has been associated with a higher risk of high-degree AV block and sudden death due to electromechanical dissociation.[56]

The use of pacemakers for stimulation due to severe bradyarrhythmias is common in this disease, being more predominant in ATTRv (up to 30%) and slow atrial fibrillation is reported as the most frequent diagnosis.[44]

QT interval prolongation: in CA, there is a prolongation of the QT interval. In patients with increased LV wall thickness, with a corrected QT interval above 440 ms with a Sokolow Lyon index less than 1.5 mV, it has a sensitivity of 85% and a specificity of 100% to detect cardiac amyloidosis *(Table 4 and Figure 3)*.[57]

Echocardiography

In patients with CA, the following echocardiographic morphological and functional features are observed:

1. Increased thickening of the left ventricular (LV) walls with a diffuse mottling, reminiscent of the typical «ground glass» image, as well as of the right ventricular (RV) walls. The increased thickness and stiffness of the myocardial wall only partially explains the ventricular dysfunction, which is also due to the effects exerted by amyloid deposition in terms of abnormal cytoarchitecture, subendocardial ischemia and direct cytotoxic effect. The latter effect is mainly caused by free light chains in the AL form. This abnormal echotexture (echo-bright or «sparkling» appearance) has frequently been associated with amyloidosis, although it is not a highly sensitive sign and its absence should not deter further diagnosis. In M-mode, the basic findings described are symmetrical enlargement of the ventricular walls in the absence of hypertension or aortic valve disease, hypokinesia and decreased thickening of the interventricular septum and the posterior wall of the left ventricle, and abnormally small size of the ventricular cavity with or without pericardial effusion, usually mild. Additionally, a septal/posterobasal free wall ratio of < 1.3, an increased maximum left atrial dimension, a reduced mitral closure slope (E-F points) and preserved left ventricular ejection fraction (LVEF) are also described. Regarding the cut-off point for diastolic ventricular wall thickness that should be considered indicative of CA, it is 12 mm, which has shown greater sensitivity, although low specificity.[49]
2. Thickening of the interatrial septum and/or valves. Infiltration of the valves is very common. Today, the coexistence of aortic

Table 4: Recommendations on the use of electrocardiogram in cardiac amyloidosis.

Recommendation	Class of recommendation	Levels of evidence
An ECG should be performed in all patients suspected of CA	I	B
The most common ECG findings of CA are low voltage-to-mass ratio (measured by maximum left ventricular wall thickness), pseudoinfarction pattern, presence of atrioventricular block, and prolongation of the corrected QT interval	I	B

CA = Cardiac Amyloidosis. ECG = Electrocardiogram.

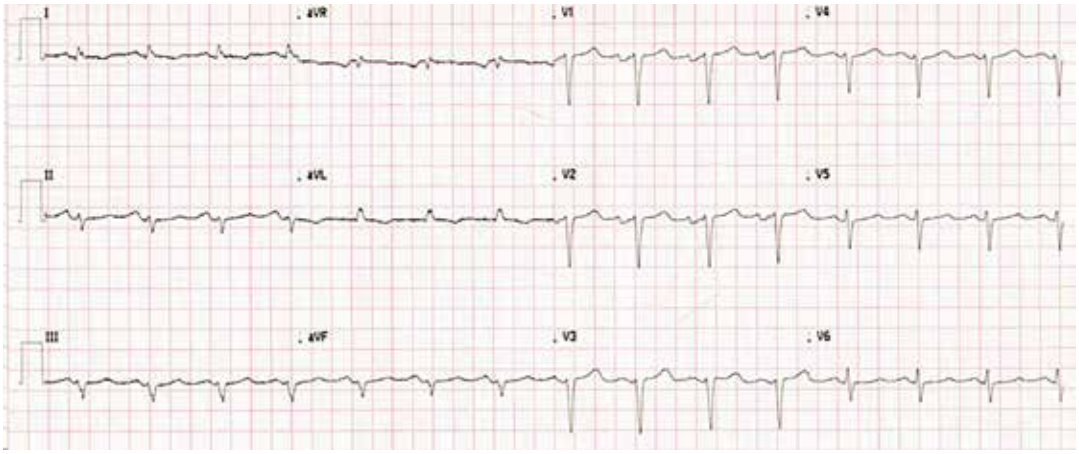

Figure 3: ECG of a patient with ATTRv. Microcomplexes are observed in the frontal plane leads, first-degree AV block, pseudo-infarct pattern in inferior and anteroseptal leads, QTc interval of 440 ms and low voltage-to-mass (interventricular septum with diastolic thickness of 15 mm).

stenosis and CA is described in up to 30% of patients, which requires studying red flags of the association and which we will describe later.

3. Presence of pericardial effusion (most often small/without hemodynamic importance) is more frequent in light chain CA as opposed to ATTR.
4. Diastolic dysfunction of (≥ grade 2) with elevated LV filling pressures in late stages of the disease. The «red flag of the rule of 5» refers to the decrease in the velocity of the s', e' and a' waves in the mitral annular tissue Doppler. It is important to emphasize that this red flag occurs in the late stages of the disease. However, the initial affectation in diastole consists of a decrease in the compliance of the ventricle that echocardiographically translates into a decrease in flow in the protodiastolic phase (velocity of the E wave of the transmitral flow) and an increase in the telediastolic phase (velocity of the A wave) due to an increase in the atrial contribution to ventricular filling. Subsequently, as ventricular distensibility continues to decrease, interatrial pressure increases, leading to an increase in the protodiastolic filling and a decrease in the atrial contribution. Finally, a restrictive pattern with a short E wave deceleration time of (≤ 150 ms) and a low A wave velocity is expected. Tissue Doppler will show a decrease in both diastolic velocities (e' and a') from early stages of the disease. Prolonged isovolumetric contraction and relaxation times with shortened ejection periods will also be found.[28,58] With restricted ventricular filling, there is a greater dependence on atrial contraction in the late diastolic phase, so atrial dysfunction further compromises ventricular filling and results in worsening of symptoms. The presence of left atrial dysfunction in patients with CA constitutes the first manifestation of cardiac involvement in patients, even in the absence of other echocardiographic manifestations. In fact, this atrial stiffness has motivated many research works regarding the reservoir function of the left atrium. When it is reduced, even in the absence of AM (atrial myopathy), it may be time to start anticoagulation. As we know, the left atrium has three functions. It acts as a reservoir during ventricular contraction and isovolumetric relaxation; as a conduit for the passive passage of blood into the ventricle; and as a pump, which represents 15 to 30% of cardiac output. Historically, atrial function has been assessed using techniques that have advanced as echocardiography has progressed, including linear measurements, two- and three-dimensional volumetric

measurements, spectral Doppler and tissue Doppler, and finally, deformation. Of these, linear methods are currently in disuse and are no longer mentioned in the latest guidelines of the American Society of Echocardiography or the European Association of Cardiovascular Imaging. Left atrial reservoir strain has gained relevance in recent years and remains a fundamental pillar for evaluating filling pressures.

5. Dilation of right cavities. Involvement of the right ventricular walls. It is associated with more severe infiltration and a worse prognosis (median survival of fourt months). A ratio of LV/RV areas of ≤ 2 is an independent predictor of survival.[59,60]
6. Myocardial deformation: regarding the new techniques, in addition to helping diagnose subclinical or early systolic dysfunction, they are useful for differential diagnosis with other causes of cardiomyopathies or increased wall thickening, such as hypertensive heart disease or hypertrophic cardiomyopathy. Initially, patients commonly have preserved LVEF, however, systolic tissue velocity, longitudinal deformation, and longitudinal deformation rate are decreased from initial stages due to initial involvement of the subendocardium. It has also been reported that segments with decreased deformation are indicative of amyloid infiltration, which is confirmed by magnetic resonance.
   The classic relative apical gradient sign (RELAPS or RAG) was originally described by the group of Pheland and collaborators,[59] where it was found that in those patients with CA there is a decrease in the basal longitudinal deformation with respect to the deformation in the apical segments.

$$RAG = \frac{\text{GLS apical average}}{\text{GLS baseline average} + \text{GLS medial average}}$$

This index is a classic red flag for CA. It is obtained by dividing the average GLS of the apical segments by the sum of the average GLS of the basal segments and the middle segments. When it is greater than 1, it presents a sensitivity of 93% and a specificity of 82% in the detection of CA. The preservation of the apical strain is characteristic of both AL and TTR cardiac amyloidosis. However, it is important to remember that the RAG is a sensitive but non-specific sign, since it can be present in other pathologies such as aortic stenosis or chronic renal failure.

Pagourelias et al.[172] introduced the ratio of the ejection fraction and the global longitudinal strain (EF/GLS) as a reliable tool to diagnose CA and confirmed that it is currently the most specific (91.7%) and sensitive (89.7%) echocardiographic parameter in the diagnosis of CA. The relationship between ejection fraction and GLS is based on the discrepancy due to the deep affectation of the subendocardium by infiltration and despite this, LVEF is preserved until advanced stages of the disease. This relationship between these variables is maintained even when LVEF falls, with a quotient of > 4.1 highly compatible with CA compared to other cardiomyopathies such as HCM, where it is classic to find this quotient to be less than 3.[59]

7) Myocardial work indices: regarding new parameters of ventricular mechanics, myocardial work (MW) indices are significantly lower in patients with CA compared to the control group, reflecting the significant impairment of myocardial performance detectable in CA. Myocardial work analysis has shown that GWE of < 86.5% identified patients with AL amyloidosis with a sensitivity and specificity, respectively, of 80.0 and 66.7%.[61] Palmiero[62] found that Global Work Efficiency (GWE) was lower in patients with AL-CA compared to patients with ATTR-CA, implying that myocardial dysfunction in patients with AL-CA is more evident. He also documented that AL-CA and ATTR-CA could be appropriately distinguished when GWE was < 86.5%, with a sensitivity and specificity of 80.0 and 66.7%, respectively. When myocardial constructive work (GCW) is < 1,039 mmHg%, the risk of all-cause mortality in patients with CA was significantly increased with a hazard ratio of 6.4 (95% HF: 2.4-17.1). Low GWE is a potential predictor of adverse cardiovascular events in patients with CA, and patients with GWE of < 89% face a high risk of all-cause mortality *(Table 5 and Figure 4)*.[61,63]

Magnetic resonance

Cardiac magnetic resonance (CMR) provides structural information and tissue characterization. For this reason, it has become a versatile tool for the study of cardiac amyloidosis (CA) through a wide range of qualitative and quantitative parameters that allow to accurately determine the diagnosis, prognosis and progression of the disease in this group of patients. Late gadolinium enhancement (LGE) represents the cornerstone in the diagnosis of CA by CMR, and it has demonstrated a sensitivity of 85% and a specificity of 92% (area under the curve = 0.95) for the diagnosis.[64] The characteristic pattern has a global subendocardial or diffuse transmural distribution, associated with alterations in the kinetics of the contrast medium. The degree of

Table 5: Recommendations on the use of echocardiography in cardiac amyloidosis.

Recommendation	Class of recommendation	Levels of evidence
Transthoracic echocardiography with global longitudinal strain measurement should be performed in all patients with suspected CA	I	B
The most frequent ECG findings of CA are left ventricular hypertrophy, intramyocardial «mottled» image, diastolic dysfunction with increased filling pressures, the presence of pericardial effusion, leaflet thickening, hypertrophy of the interventricular septum and/or the right ventricle, and a global deformation pattern with an apical-basal gradient («Cherry on top» image)	I	B
The cut-off point for diastolic ventricular wall thickness for suspected CA is 12 mm	I	B

CA = Cardiac Amyloidosis. ECG = Electrocardiogram.

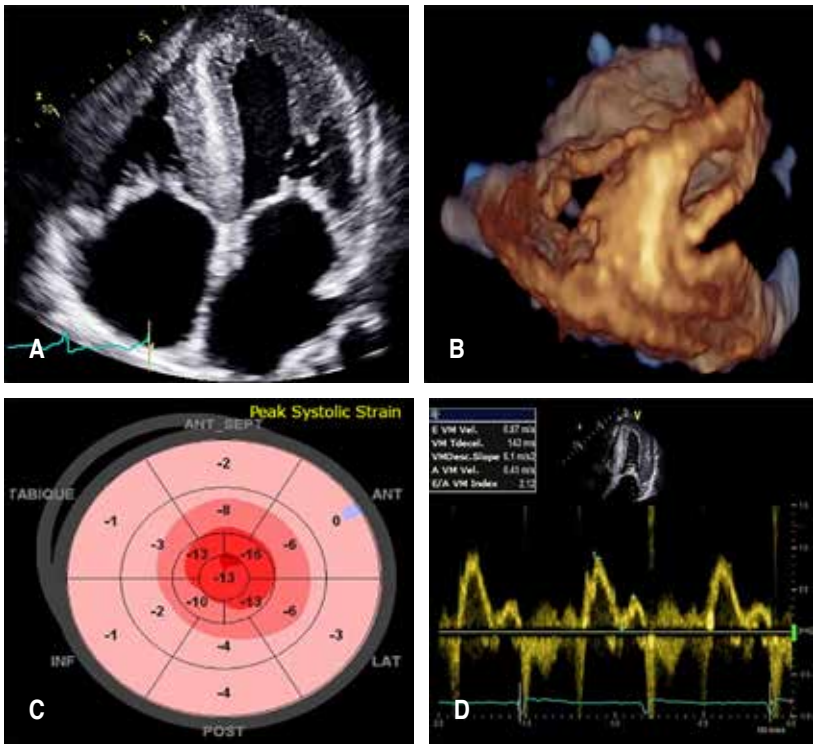

Figure 4:
A) Apical 4-chamber view showing thickening of the valves, the interatrial septum and both ventricles, with an intramyocardial «mottled» image. **B)** Three-dimensional image of the tricuspid valve showing thickening of the 3 leaflets, suggesting infiltration. **C)** Classic images where RELAPS is greater than 1, great deterioration of the basal deformation with preservation of the apex, giving that classic «cherry on top» appearance. **D)** The restrictive filling pattern is observed. RELAPS = Relative Apical Gradient.

transmurality has been directly associated with the severity and prognosis of the disease,[65] while the extension of the LGE to the atria and right ventricle would be more frequent in ATTR-CA.[66]

T1 parametric mappings are sequences with important advantages in terms of identifying fibrosis in a quantitative and early manner, especially in patients with contraindications for the use of contrast media. T1 mapping is elevated from early stages, even prior to the development of ventricular hypertrophy or detection of LGE, with a cut-off point of 1140 and 1341 milliseconds for studies in 1.5 and 3 Tesla equipment, respectively.[67]

The calculation of extracellular volume (ECV) by means of post-contrast T1 mapping of > 40% directly correlates with severity and prognosis. Higher values are found in cases of ATTR-CA. Currently, it is the technique used for quantifying the intramyocardial amyloid deposit load, in addition to its relevance in the follow-up and monitoring of response to treatment.[68]

Cardiac MRI has established itself as a reproducible and highly accurate imaging modality for the diagnosis and monitoring of patients with CA, however, it does not characterize between ATTR and AL *(Table 6 and Figure 5)*.

Scintigraphy

Scintigraphy (or gammagraphy) is a nuclear medicine and molecular imaging study that uses Technetium-99m(99mTc)-labeled phosphonates and is currently the cornerstone for noninvasive diagnosis and characterization of ATTR.[63,69-72] It is the first imaging method to be affected, allowing for very early detection, even in asymptomatic patients with no morphological or functional changes.[71] There are three radiotracers that can be used: pyrophosphates (99mTc-PYP); 99mTc-3,3-diphosphono-1,2-propanedicarboxylic acid (99mTc-DPD); and 99mTc-hydroxymethylene diphosphonate (99mTc-HMDP). There are some differences in their structure and mechanism, however, their uses are currently standardized and can be used depending on availability.[69,70,72] Methyl diphosphonate (99mTc-MDP) is not indicated in any case, due to its low sensitivity, which can cause false negatives.[73]

No special preparation is required for the study and static images of the chest should be acquired in anterior, left anterior oblique and left lateral projections (at 750,000 counts/image), as well as a single-photon emission computed tomography (SPECT) of the chest (40 images, 20 seconds/image, 90º angle).[69,74,75] The latter is mandatory (not optional) to increase diagnostic certainty and reduce false positives. If a hybrid study (SPECT/CT) is available, it should be preferred over simple SPECT.[69,70,74,76]

Interpretation

1. Semi-quantification of the ***Perugini Score***: visual comparison of the myocardium with respect to the bone uptake of the ribs.

    a. Grade 0: no myocardial uptake.
    b. Grade 1: smaller uptake than that of the ribs.
    c. Grade 2: equal uptake to that of the ribs.
    d. Grade 3: greater uptake than that of the ribs.

    A grade 0-1 is classified as low probability for ATTR, while a grade 2-3 is classified as high probability.

2. *Heart to contralateral lung ratio* (**H/CL ratio**): it is assessed on the previous static image, and it is the ratio of the count of a region of interest (ROI) of the heart to the count of a ROI of the contralateral hemithorax. An H/CL ratio of ≥ 1.5 on the 1-hour image or of ≥ 1.3 on the 3-hour image is classified as highly suggestive of ATTR.
3. SPECT or SPECT/CT: in axial, coronal and sagittal sections, it is confirmed that the uptake of the radiotracer is in the walls of the left ventricle (LV) (specific data of cardiac amyloidosis), while, if the uptake is observed within the cavity, this corresponds to a blood «pool» (false positive in the previous static image).[69,70,72,77-80]

Uptake of grade 2-3 on the Perugini score and H/CL of > 1.5 on a 60-min image or of > 1.3 on a 180-min image are highly suggestive of TTR-CM *(Figure*

Table 6: Recommendations on the use of cardiac magnetic resonance imaging in cardiac amyloidosis.

Recommendation	Class of recommendation	Levels of evidence
Cardiac magnetic resonance imaging with gadolinium is recommended in patients with suspected CA	IIa	B
The most common CMR findings in CA are left ventricular hypertrophy, late subendocardial or transmural enhancement, and increased T1 and extracellular volume	IIa	B
Cardiac magnetic resonance imaging should be performed in cases of suspected diagnosis, with negative scintigraphy and light chain study, in the absence of monoclonal gammopathy	IIa	B

CA = Cardiac Amyloidosis. CMR = Cardiac Magnetic Resonance.

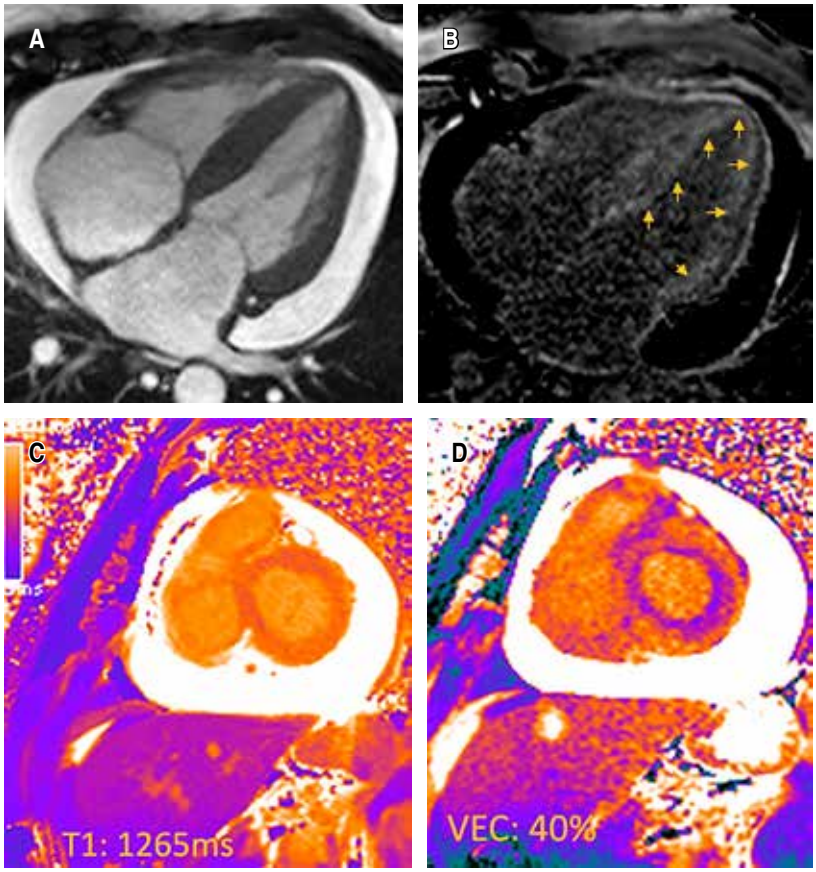

Figure 5: Magnetic resonance imaging in a patient with AL-CA. **A)** LV hypertrophy and pericardial effusion are observed. **B)** Global subendocardial late enhancement image. **C)** Increased native T1. **D)** Increased extracellular volume. AL = Light-chain Amyloidosis. CA = Cardiac Amyloidosis.

1). However, it must be considered that up to 20% of AL amyloidosis can capture 99mTc-phosphonates, therefore, a complete evaluation with light chains (quantification/ protein and immunofixation electrophoresis of blood and urine) should be carried out to exclude this diagnosis.[63,70,72,74,81] A negative scintigraphy does not exclude the diagnosis completely. Among the causes of false negatives, consider non-phosphonate-avid hATTR variants.[72,76,79] A positive scintigraphy does not exclude AL and can only be concluded as positive for ATTR in the absence of monoclonal gammopathy.

In a patient where monoclonal gammopathy has been previously excluded, a grade of ≥ 2 scintigraphy in the SPECT scan confers a sensitivity, specificity, and positive predictive value of 100%.[81-83] In cases where AL-CA has not been adequately excluded, the specificity decreases to 82-86%.[83] Gilmore et al.[84] reported a positive predictive value of 100% (95%HF, 98.0-100%) in patients with compatible or suggestive ECHO or CMR of CA and absence of monoclonal gammopathy. Performing serial follow-up scans to assess disease progression and response to treatment is not recommended because it is still under study and requires further evidence.[83]

Although the evidence indicates the diagnostic power of scintigraphy of ≥ grade 2 assessed in SPECT (for ATTR), it must be considered that no degree of uptake (Score grade 1) is physiological and, if it is corroborated in all sections (coronal, axial and longitudinal), it should be considered abnormal *(Table 7 and Figure 6)*.

DIAGNOSIS

Traditionally, amyloidosis was considered a «rare» disease. With advances in cardiac imaging and new disease-modifying therapies, we know that cardiac amyloidosis is a frequent cause of underdiagnosed heart failure.

The most decisive step for diagnosis is suspicion of the disease. Cardiac amyloidosis is known as the great imitator because it is a systemic disease that involves multiple organs and a great heterogeneity of symptoms that vary from patient to patient. It has been studied that up to 20% of patients with amyloidosis have made up to 5 visits to different specialists until they were given the correct diagnosis. Furthermore, up to 50% of patients with hATTR and 39% with ATTRwt received an erroneous diagnosis, and most of these patients received treatment for that condition. This can be harmful, since generally the conventional treatment for heart failure in these patients is harmful.[85]

Suspicion should be based on the clinical characteristics of the patients and the appropriate use of diagnostic tools (electrocardiogram, echocardiography, magnetic resonance imaging). *Figure 7* shows the diagnostic algorithm, which is summarized in 4 steps, which are detailed below *(Table 8)*:

Step 1: it should be based on clinical suspicion *(Figure 2)* or on studies such as ECG, echocardiogram or magnetic resonance imaging.

Step 2: the next step is to rule out AL-CA, initially requesting the following studies:

1. Serum free light chain.
2. Serum and urine protein electrophoresis with immunofixation.

Regarding the analysis of free light chains, the Kappa/Lambda ratio must be calculated, which presents normal values depending on the patient's glomerular filtration rate (GFR) as follows:

In case of negative values of κ/λ ratio, AL-CA is ruled out. In case of positive results of κ/λ ratio, this may or may not be due to monoclonal gammopathy, so IFE of proteins of blood or urine is needed. For the proper interpretation of the latter, the patient should be referred to a hematologist, who will confirm the diagnosis with a bone marrow or tissue biopsy. The interpretation of results can be a very big challenge since monoclonal gammopathy of undetermined significance (MGUS) is relatively frequent in patients with ATTR (5-39%).[1,86]

Step 3: after ruling out AL-CA, phosphate scintigraphy is performed. In case of negative results (uptake G°0-1), it should be assessed whether the high diagnostic suspicion persists. Cardiac magnetic resonance is recommended if it has not been performed previously. If this is the case, a biopsy is performed, otherwise, the diagnosis of CA is ruled out.

Amyloid fibril is observed as a homogeneous eosinophilic interstitial substance with hematoxylin-eosin staining under the light microscope. When using Congo red staining, it binds to the beta-pleated structure of amyloid, which produces a pathognomonic apple-green birefringence when observed under polarized light. It is recommended to collect tissue from at least 4 sites of the endocardium.[86]

The goal of the biopsy, in addition to documenting amyloid infiltration, is to provide a definitive histological etiology by identifying

Table 7: Recommendations on the use of scintigraphy in cardiac amyloidosis.

Recommendation	Class of recommendation	Level of evidence
Phosphonate scintigraphy should be performed in patients with suspected CA	I	A
SPECT imaging is mandatory to ensure diagnostic certainty by confirming that uptake is located in the LV walls	I	A
Perugini score grade 2-3 uptake and H/CL of > 1.5 in 60-min image or of > 1.3 in 180-min image are highly suggestive of TTR-CM[1]	I	A

CA = Cardiac Amyloidosis. H/CL = Heart to Contralateral Lung ratio. LV = Left Ventricle. SPECT = Single-Photon Emission Tomography. TTR-CM = Transthyretin amyloid cardiomyopathy.

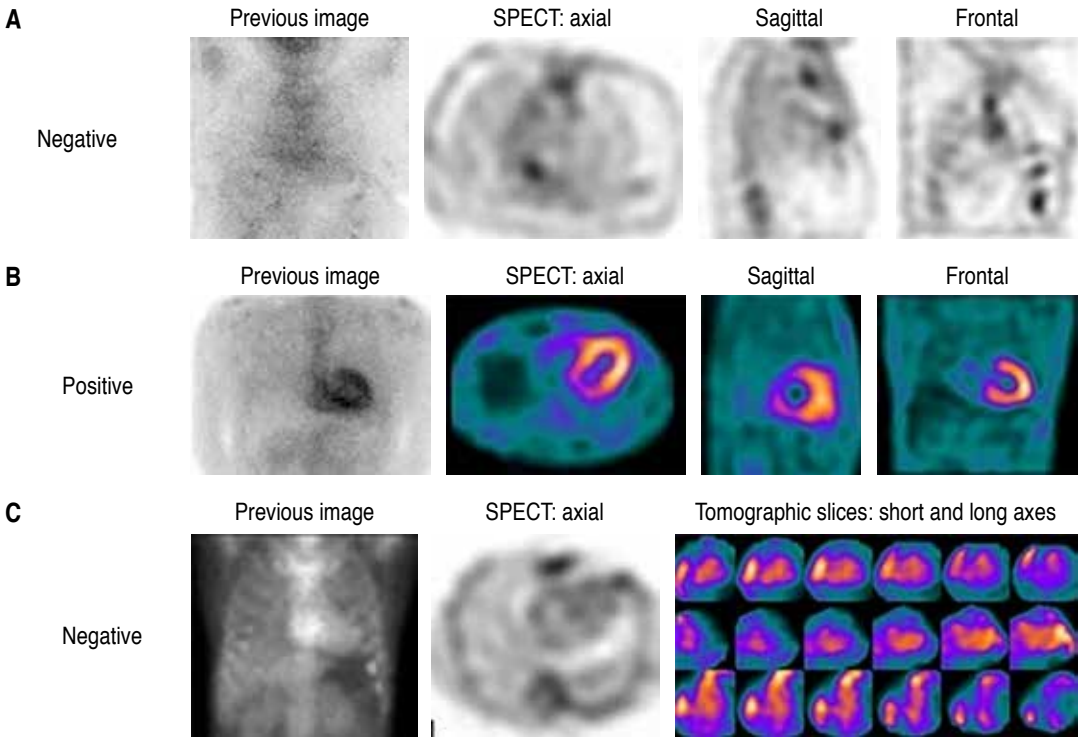

Figure 6: ATTR scintigraphy images. 99mTc-Pyrophosphate scintigraphy in patients with suspected ATTR, images at 180 minutes. Row **A)** ATTR-negative scintigraphy (Perugini 0, H/CL 1.22, SPECT without uptake). Row **B)** ATTR-positive scintigraphy (Perugini 3, H/CL 1.52, SPECT with uptake in LV walls). Row **C)** ATTR-negative scintigraphy (the static image seems to capture myocardial topography, but when reviewing the tomographic sections, it shows that it is actually a blood «pool», and there is no uptake in the LV walls. This study without SPECT analysis could be considered a false positive).
ATTR = Transthyretin Amyloidosis. H/CL ratio = Heart/Contralateral Lung ratio. LV = Left Ventricle. SPECT = Single-Photon Emission Tomography.

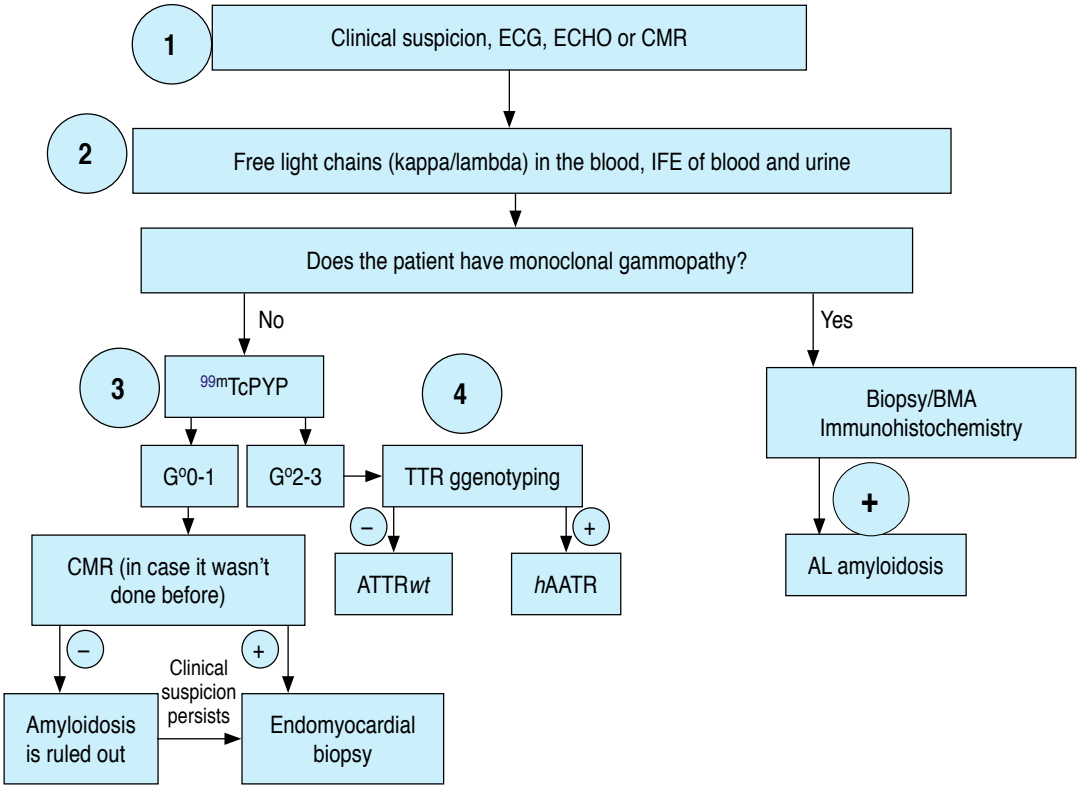

Figure 7: Diagnostic algorithm for cardiac amyloidosis.
BMA = Bone Marrow Aspiration. CMR = Cardiac Magnetic Resonance. ECHO = Echocardiogram. ECG = Electrocardiogram. IFE = Immunofixation Electrophoresis. 99mTcPYP = 99mTechnetium pyrophosphate.

Table 8: Analysis of free light chains in the blood.[1]

GFR (mL/m)	K/L (κ/λ) ratio	Consider positive if
> 60	0.26-1.65	≥ 1.65
45-60	0.46-2.62	≥ 2.62
< 45	0.48-3.38	≥ 3.38

GFR = Glomerular Filtration Rate.

the protein responsible for it. There are two possible methods:

1. Immunohistochemistry with light microscopy, along with the use of antibodies, is the most widely available method to typify the fibrils. Its diagnostic value is high in most cases of ATTR amyloidosis; however, its specificity is very low. Caution should be taken when using this method, as in patients with AL the results are often not definitive due to high rates of false positives in transthyretin antibody staining and low sensitivity for light chain staining.[1,87]
2. Mass spectrometry can overcome these limitations because this method is antibody-independent, which makes it the «gold standard» for classifying fibrils. Diagnosis is made after using laser microdissection of positive Congo red stained slides. The major disadvantage of this method is that it is not widely available everywhere.[1,87]

Extracardiac biopsy

The main sites for the biopsy procedure are abdominal fat, bone marrow, gums, skin, salivary gland or gastrointestinal tract (rectum). The biopsy procedure has a higher diagnostic yield in AL amyloidosis than in ATTR (due to

high false negative rates). The sensitivity of the extracardiac biopsy is particularly low for ATTRwt.

Step 4: if ATTR is confirmed (by scintigraphy or biopsy), all patients (regardless of age) should undergo a TTR sequencing study. The result should be discussed in genetic counseling (geneticist).

TREATMENT

Heart failure treatment

Heart failure (HF) is a clinical syndrome that has become one of the main cardiovascular health problems in the world. This is due to its high prevalence (1-3% of the adult population). Its incidence is rising. The life prognosis is adverse (50% mortality rate at five years from clinical diagnosis) with high costs of outpatient and hospital care. Therefore, an early, accurate and comprehensive diagnosis of this condition is required to improve the clinical course and prognosis of patients.[88]

As a syndrome, HF is the result of multiple nosological entities. In the case of amyloidosis, current data estimates that this disease is responsible for 10% of all cases of HF with reduced and mildly reduced LVEF, while for patients with HF with preserved LVEF, amyloidosis may be the cause of 6 to 30% of all cases.[15,32,89]

In recent studies, it has been reported that the prevalence of amyloidosis in patients hospitalized for heart failure is 8.17 × 10^0,000 people/year with an incidence of 18-55 × 10^0,000 people/year, and is more frequent in men, geriatric population and people of African descent.[90]

From the above, it follows that amyloidosis is a more frequent clinical entity than assumed, so it should be suspected in the diagnosis and comprehensive evaluation of patients with heart failure.

Heart failure is the most common manifestation of cardiac involvement in amyloidosis. It comes in the form of pseudohypertrophic restrictive cardiomyopathy, which is the result of infiltration and deposition of amyloid fibers in the interstitial space of the heart, leading to structural and functional alterations ranging from diastolic dysfunction to severe myocardial damage. Therefore, it can be observed in the form of HF with preserved or reduced LVEF, although the most common phenotype is that of patients with LVEFP-HF. This condition can occur in patients with light chain amyloidosis as well as in ATTR amyloidosis (Hereditary and Wild-Type).[91]

The clinical picture of heart failure in patients with amyloid cardiomyopathy does not differ significantly from that observed in other causes of HF. The most important data are fatigue, dyspnea on exertion, and pulmonary or systemic congestion. However, it is noteworthy that, in these patients, clinical data is found that is highly characteristic of etiology and involves a tendency to hypotension, dysautonomia, arrhythmias, fainting and syncope. These symptoms are part of the red flags within the initial evaluation and clinical suspicion of cardiac amyloidosis.[91]

Therapeutic objectives

Once the clinical, electrocardiographic, imaging, histopathological and genetic diagnosis has been made (see corresponding sections), the therapeutic objectives of patients with amyloid cardiomyopathy and heart failure should include:

1. Symptom control and improvement in quality of life.
2. Reduction of episodes of worsening heart failure (with or without hospitalizations).
3. Improvement of survival.
4. Cost control.

For this purpose, there are two types of treatment: one aimed at managing heart failure as a syndrome (conventional treatment) and disease-modifying therapies (amyloidosis).

Conventional treatment

Regarding non-pharmacological measures, there is insufficient and not strong evidence to make specific recommendations on nutrition or physical activity in patients with heart failure due to amyloidosis. Therefore, it is reasonable to apply the same principles for heart failure

in general, considering that, and due to the tendency to hypotension and dysautonomia, special care must be taken to avoid volume depletion.

Although today the quadruple therapy (sacubitril-valsartan/ACE inhibitors/angiotensin receptor blockers + betablockers + mineralocorticoid receptor antagonists + SGLT2i) is fully accepted as the fundamental management of HF with reduced LVEF and the use of SGLT2 inhibitors as the cornerstone of the treatment of HF with preserved and slightly reduced LVEF. In the case of HF due to amyloidosis, the evidence of the usefulness and safety of these drugs is debatable.[83,91-93]

Because congestion is a common finding in HF secondary to amyloid cardiomyopathy, the use of diuretics has become the cornerstone of pharmacological treatment. Currently, evidence points to the usefulness of the combination of loop diuretics plus mineralocorticoid receptor antagonists as the basic therapy in patients with HF due to amyloidosis, regardless of LVEF. Regarding the type of loop diuretics, the use of Bumetanide or Torasemide is preferred over Furosemide due to their better pharmacokinetic profile. It is important to note that, due to restrictive hemodynamics, these patients are particularly sensitive to sudden changes in intravascular volume, so the dose of diuretics should be adjusted to the individual needs of each patient and data on volume depletion or residual congestion should be closely monitored.[83,91,92]

In the case of sacubitril/valsartan, there is no evidence from randomized clinical trials on its efficacy in patients with cardiac amyloidosis. Furthermore, due to the tendency to hypotension, the use of this drug in patients with HF with reduced LVEF and amyloidosis should be prescribed and monitored carefully to avoid episodes of severe hypotension with deleterious effects on cardiac output. This same phenomenon occurs with ACE inhibitors and angiotensin receptor blockers.[83,91,92]

Heart rate control, prevention of sudden death and control of sympathetic overactivity are arguments in favor of making betablockers part of the essential therapy of HF with reduced LVEF. In addition, they can be used to control heart rate or relieve angina in patients with atrial fibrillation or HF of ischemic origin regardless of LVEF. However, in the case of HF caused by amyloidosis, these drugs are usually poorly tolerated. In fact, poor tolerability or significant worsening of symptoms in a patient with reduced LVEFP-HF who starts betablockers may be an indication that the cause of heart failure is amyloidosis. This is because the increase in heart rate is a compensatory mechanism in patients with restrictive hemodynamics, so reducing it can cause significant alterations in cardiac output (CO) and worsening of symptoms. In addition, there is no reliable evidence of the usefulness of betablockers to reduce sudden death in patients with cardiac amyloidosis.[83,91,92]

SGLT2i are drugs that have demonstrated their usefulness across the entire spectrum of heart failure and are well tolerated. An exploratory study in patients with HF due to ATTR amyloidosis treated with Tafamidis demonstrated that the addition of Dapagliflozin was well tolerated and contributed to decreasing NT-proBNP levels, suggesting the usefulness of these drugs in this clinical scenario.[93] Recently, Porcari et al. performed a retrospective analysis of 2,356 patients with cardiomyopathy due to TTR amyloidosis, of which 11% received treatment with SGLT2i (dapagliflozin or empagliflozin) and found a favorable trend with the use of these drugs regarding functional class, renal function and diuretic requirement.[94] However, clinical studies with a larger number of patients are needed to be able to define the role of SGLT2i in patients with amyloidosis and heart failure.

Digoxin plays a controversial role, since, on the one hand, it helps control the ventricular response in patients with HF due to amyloidosis in atrial fibrillation, but on the other hand, the binding of this drug to amyloid fibers could have a deleterious effect on the progression of the disease. For this reason, its use is at the discretion of the treating physicians who must carefully weigh the risk-benefit ratio and, if it is decided to start the cardiac glycoside, it is recommended that it be at low doses and with electrocardiographic monitoring and serial digoxin serum levels.[83,91,92]

Calcium antagonists are poorly tolerated due to their negative inotropic and chronotropic

effects, as well as their vasodilatory properties. Similarly, non-dihydropyridine calcium antagonists increase the risk of conduction blocks.[83,91,92] In turn, there is no evidence of any benefit in these cases, so their use is not recommended.

In patients with heart failure due to amyloidosis and severe symptomatic hypotension, the use of midodrine may be an option to consider.[92]

In conclusion, the management of heart failure due to amyloidosis represents a challenge for clinicians, since conventional tools are not an option that guarantees benefits, as in the case of heart failure due to other causes. For this reason, it is necessary to have specific therapies that slow the progression of structural and functional damage and can favorably modify the clinical course of patients.

Table 9 summarizes the indications for «conventional» treatment of heart failure in patients with amyloidosis.

Atrial fibrillation and embolism

Abnormal protein deposition in the extracellular space of the heart muscle causes electromechanical dysfunction of the atria and ventricles.[28,95,96] In the atria, it causes atrial cardiomyopathy (ACM) that predisposes to contractility and conduction disorders such as interatrial blocks, atrioventricular blocks, and favors rhythm disorders, particularly atrial fibrillation (AF).[28,96,97] In the ventricles, it causes enlargement, ventricular stiffness, and intra and interventricular conduction disorders and potentially lethal ventricular arrhythmias. These changes in stiffness cause ventricular restrictive cardiomyopathy, which also contributes to left atrium (LA) dilation and disease.[96-98] AF is associated with CA in 15-88% of patients, depending on the study group analyzed, type of fibrillation, and stage of CA.[28,96-100] It is more often found in transthyretin amyloidosis (TTR-CA) than in light chain amyloidosis (AL amyloidosis). Of the TTR-CA group, AF is more prevalent in the wild-type than in the hereditary type. Renal failure, heart failure, age, male gender, reduced left ventricular ejection fraction and left atrium dilatation are independent risk factors for the relationship.[96,97,100]

CA is associated with a high incidence of thrombi in patients with or without AF, regardless of the type of CA. Pathology studies of patients with CA have reported thrombi in 8-33% of cases. These thrombi are located not only in the left atrial appendage, but also in the body of the left atrial appendage, even in the right atrium and ventricles. A patient may even have more than one thrombus.[96-101] Mortality associated with thromboembolic events (TEEs) is reported in patients with CA

Table 9: Pharmacological management proposal for heart failure in patients with cardiac amyloidosis.

Recommendation	Class of recommendation	Level of evidence
Loop diuretics to reduce pulmonary or systemic congestion	I	C
ARNIs/ACEI/ARBs to reduce the risk of hospitalizations or cardiovascular death	IIB	C
Betablockers to reduce the risk of hospitalizations or cardiovascular death	III	C
Mineralocorticoid receptor antagonists to decrease pulmonary or systemic congestion (in conjunction with loop diuretics)	I	C
SGLT2 inhibitors to reduce the risk of hospitalizations or cardiovascular death	IIA	C
Digoxin for heart rate control in patients with atrial fibrillation with accelerated ventricular response	IIB	C
Calcium antagonists to reduce the risk of hospitalizations or cardiovascular death	III	C
Midodrine for the management of severe symptomatic hypotension	IIB	C

ACEI = Angiotensin-Converting Enzyme Inhibitors. ARBs = angiotensin-receptor blockers. ARNIs = angiotensin receptor-neprilysin inhibitor. SGLT2 = Sodium-Glucose Cotransporter Type 2.

of 8%.[100] A multicenter European study of 1,191 patients with TTR-CA, of which 83% were wild-type, in a follow-up of almost 20 months, reported a rate of thromboembolic events ranging from 16% on average.[102] In this same study, the incidence of thromboembolic events in patients with TTR-CA in sinus rhythm with anticoagulation was 0 events. In patients in sinus rhythm without anticoagulation, the rate was 1.3 events per 100 patients per year. In the group of patients with AF and oral anticoagulation, the rate was 1.7 events per 100 patients per year. In the group of patients with AF without anticoagulation, it was 4.8 events per 100 patients per year, so that OAC plays a primary role in the prevention of TEEs.[102] Another study reports a 20% incidence of TEEs in patients with AF versus 9% in patients without AF, that is, sinus rhythm does not ensure the absence of thrombi or of these TEEs. Certainly, AF in these patients contributes significantly to the formation of intracardiac thrombi, particularly in the left atrium. However, there are other factors that favor the formation of a thrombus. Electromechanical dysfunction or atrial myopathy caused by CA will favor a deterioration of left atrial contractility, blood ectasia and turbulent flow, phenomena related to thrombus formation.[96,97,100] Ventricular dysfunction also contributes to atrial damage by increasing left atrium pressure and growth.[102] On the other hand, these proteins have a direct toxic effect on the cardiac muscle that can activate the inflammation cascade and an increase in prothrombotic phenomena, which together with the structural anomalies mentioned, usually cause the formation of clots inside the heart, which can result in a cerebrovascular or systemic event of cardioembolic origin.[97,102]

Early detection of these patients becomes a medical priority for the timely initiation of oral anticoagulation (OAC). In patients with AF without CA, AF management guidelines recommend the use of the CHA_2DS_2VASc risk score to identify patients at medium and high risk of thromboembolic events (TEEs).[103-105] However, in patients with CA and AF, the CHA_2DS_2VASc score does not have the power to detect risk. In one study, they analyzed 100 patients who were candidates for electrical cardioversion due to AF. They performed a transesophageal echocardiogram and found a thrombus in 30 patients. They applied the CHA_2DS_2VASc score to them, and they found that low-risk patients (1 to 2 points) had a higher proportional incidence of thrombi than those with a higher score of (> 3 points). They also found that previous use of anticoagulants does not prevent thrombus formation. This work concludes that, in patients with CA and AF, the CHA_2DS_2VASc score is not useful to detect patients at risk of thrombus formation and that oral anticoagulation does not guarantee the absence of thrombus. Therefore, this risk score should not be used, and a transesophageal echocardiogram should be performed before electrical cardioversion, regardless of the type of AF and the use of previous anticoagulants. It also suggests the use of anticoagulants in all patients with CA and AF if the risk of bleeding is not prohibitive.[28,100,103-105] Currently, the recommendations of most treatment guidelines and published works regarding oral anticoagulation in patients with CA and AF consistently recommend the use of oral anticoagulants.[28,95-100,102-105] However, there is no formal recommendation to do so with vitamin K antagonists (VKAs) or with direct anticoagulants (DOACs). In the same European multicenter study mentioned above, they describe a population of 531 patients with CA, AF and OAC.[102] 57.5% of patients were taking VKAs and 42.5% DOACs. In this cohort study, the incidence of TEEs in the VKAs group was two events per 100 patients per year compared to 1.6 events per 100 patients per year in the DOACs group, with no significant difference in both groups. It should be noted that the type of OAC used in both groups is not specified. They also report that most of the TEEs in the VKAs group had an instability (lability) in the INR or a time in therapeutic range (TTR) of < 60%. This confirms the need to have a TTR of > 70% to maintain the efficacy and safety of the OAC, as in patients with AF without CA. In terms of major bleeding, there was also no significant difference with the use of OAC. The trend of OAC in these patients is in favor of DOACs due to the ease of anticoagulation and their efficacy and safety profile. Another study carried out in the United States[106] involved

Table 10: Recommendations for anticoagulation in patients with cardiac amyloidosis.

Recommendation	Class of recommendation	Level of evidence
The CHA_2DS_2VASc risk score should not be used to stratify patients with cardiac amyloidosis and atrial fibrillation at risk for cardioembolic events	III	B
The use of oral anticoagulation with vitamin K antagonists or direct anticoagulants is reasonable in patients with cardiac amyloidosis and atrial fibrillation to reduce the risk of cardioembolic events	IIA	B
The use of transesophageal echocardiography prior to electrical cardioversion is reasonable regardless of the previous use of oral anticoagulation	IIA	C
The use of oral anticoagulants in patients with cardiac amyloidosis and sinus rhythm should be individualized and agreed upon with the patient and family members	IIB	C

CHA_2DS_2VASc = Congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥ 75 (doubled), Diabetes, Stroke (doubled)-Vascular disease, Age 65–74, Sex category.

217 patients with CA and AF. They compared the use of AVKs (warfarin) in 36% of patients and OAC in 54% of patients, of which 5% received dabigatran, 21% rivaroxaban and 28% apixaban. In a 2.4-year follow-up, the incidence of TEEs per 100 patients per year was 2.9 in the warfarin group and 3.9 in the DOACs group. Although numerically the results favor warfarin, the difference was not statistically significant. Similar results were reported in terms of major bleeding.

Although there is insufficient information to validate the use of atrial appendage occluders in this population, their use in patients with high risk of bleeding and/or contraindication to OAC may be considered, particularly in patients with amyloidosis involving the brain *(Table 10)*.

Cardiac arrhythmias and devices

Implantable defibrillators-primary prevention: although cardiac amyloidosis is associated with poor prognosis and increased mortality due to heart failure, arrhythmias and electromechanical dissociation associated with sudden death (more than 50% of patients), the role of implantable cardioverter-defibrillators (ICDs) is still unclear. The standard indication for ICD placement in patients with a LVEF of < 35%, despite optimal medical treatment, is hardly applicable in patients with cardiac amyloidosis, since a low LVEF in these patients indicates a very advanced disease, in which there is already a higher risk of electromechanical dissociation as a terminal arrhythmic event. The same is true for high levels of NT-ProBNP and troponin. Although they are associated with poor prognosis, there is still no data to suggest that these biomarkers can be used to predict who may or may not benefit from ICD placement.

This is why we must consider using other tools to help us stratify the risk in these patients, such as speckle tracking and global longitudinal strain (GLS) in echocardiography or late gadolinium enhancement in magnetic resonance imaging, with the aim to detect patients in early stages of the disease and be able to discern who would be a candidate for ICD placement. However, further studies are still needed to clarify the histopathological basis of late enhancement in these patients, since late enhancement not only reflects fibrosis, but may merely be due to amyloid deposition.[107]

Many studies have aimed to investigate whether placing an ICD as primary prevention increases survival in patients with cardiac amyloidosis. To date, a clear positive impact on mortality has not been established in the literature. However, it is important to mention that most of the published reports on the efficacy of ICDs in amyloidosis come from small, observational samples with short follow-ups, so a clear recommendation cannot be given.

Kim et al.[108] conducted a case-control study to analyze survival in patients with cardiac amyloidosis with and without ICDs as primary prevention. They also compared these results with patients without cardiac amyloidosis who were similar in age, gender, and year of device implantation. In three years of follow-up, up to 26% of patients with amyloidosis received appropriate shocks. However, no significant benefit in survival was observed in those patients with amyloidosis and ICDs despite successful defibrillation therapies.[108] This means that, although ventricular arrhythmias are frequent in these patients, their presence does not seem to predict sudden cardiac death. It is thought that this is because sudden death episodes are caused by electromechanical dissociation secondary to pulseless electrical activity and extreme bradycardia.[109] For all the reasons mentioned above, the use of ICDs as primary prevention in patients with amyloidosis is not currently recommended on a routine basis, but rather each case should be individualized based on the characteristics of each patient.[28] It is unclear whether there is a clear benefit of ICD placement between the two subtypes of amyloidosis, since most of the studies carried out include patients with AL who have been shown to have more common ventricular arrhythmias and a worse prognosis.[110]

Implantable defibrillators-secondary prevention: the indication of ICDs for secondary prevention should be made according to standard indications for patients without cardiac amyloidosis and a transvenous ICD is preferred over a subcutaneous one.[82,111] ICD implantation may be considered in patients with sustained ventricular arrhythmias causing hemodynamic instability, after a careful discussion of the competing risks of death from non-arrhythmic and non-cardiac causes.[112]

Pacemaker: the natural history of the disease is associated with conduction system abnormalities of one form or another in all amyloidosis subtypes, usually manifesting with extreme bradycardias and advanced atrioventricular blocks.[111]

Most patients who develop these abnormalities will require a pacemaker, however, a distinction can be made between the different amyloidosis subtypes. Up to 30% of ATTRwt and 15% of hATTR patients have been shown to have a pacemaker implanted at the time of disease diagnosis compared to only 1% of AL patients, suggesting a different electrophysiological pathophysiology in ATTR and AL.[107] This is probably because ATTR patients are older and have a better prognosis than AL patients. In these patients, pacemaker insertion should be performed according to standard indications for patients without cardiac amyloidosis, that is, in patients with presence of advanced conduction disease defined as second-degree AV block or third-degree AV block regardless of symptoms. In addition, resynchronization therapy may be considered in those patients in whom high pacemaker dependence is expected.[113]

However, what is not yet specified is the ideal time for pacemaker placement, especially for those patients who are at high risk of developing alterations in the conduction system even without a clear conventional indication.[114] The current recommendation is to use a lower clinical threshold in these patients, since as the disease progresses, the insertion of the device allows for optimization of medication and improved exercise tolerance *(Table 11)*.[111]

Table 11: Cardiac device recommendations.

Recommendation	Class of recommendation	Level of evidence
Implantation of an automatic defibrillator should be considered in patients with a history of sustained ventricular tachycardia, ventricular fibrillation, or need for resuscitative electrical therapy	IIA	C
Pacemaker implantation should be considered in patients with advanced atrioventricular block, extreme bradycardia, or documented sinus node dysfunction	I	C

Disease Modifying Treatment or Therapies

Currently, the use of disease-modifying treatments is recommended as the only strategy to impact mortality in patients with cardiac amyloidosis. These treatments depend on the type of amyloidosis. For the purposes of this positioning, we will mention disease-modifying treatments for TTR and AL amyloidosis. In the case of AA amyloidosis, treatment is based on the management of the predisposing cause.

TTR amyloidosis

TTR amyloidosis is secondary to the infiltration of amyloid fibrillins secondary to the misfolding and disintegration of transthyretin, a quaternary protein produced in the liver. TTR amyloidosis-modifying treatments are divided into silencers, stabilizers and degraders.

RNA Silencing therapies treatments: these are drugs that function as silencers of the RNA of the TTR gene, with the decrease in the production of the TTR tetramer, both in patients with the hereditary and wild-type form. Among them, we have Patisiran and Vutrisiran. Patisiran was evaluated in a phase III clinical trial and was able to demonstrate less deterioration of the 6-minute walk and improvement in quality of life.[115] However, the study was not designed to evaluate mortality or hospitalization outcomes. Vutrisiran, a second-generation TTR RNA silencer is still being evaluated in the phase III clinical trial.

TTR stabilizing therapies treatments: these are drugs that bind to the TTR tetramer, stabilizing it and preventing its disruption into dimers (the initial step in the formation of amyloid fibrillins). These include diflunisal, tafamidis and acoramidis. Diflunisal is a nonsteroidal anti-inflammatory drug with little evidence of improved outcomes, but worsening of renal function, which is why it was discontinued in a considerable proportion.[116] Tafamidis was evaluated in phase II and III clinical trials, showing significant improvement in survival and hospitalizations. In addition, significant improvement in quality of life and less deterioration in a 6-minute walking distance were observed. These results were achieved without major adverse effects.[117] The benefit is observed after 18 months of treatment and, in the follow-up study, greater benefit is observed in patients with early onset,[118] suggesting a clear benefit in patients in early stages (NYHA class I-III) and modest in patients with late disease (NYHA IV). Recently, Acoramidis was evaluated in a phase II clinical trial, achieving similar results to Tafamidis.[119] At the moment, only Tafamidis has been approved in Mexico for use against ATTR, both hereditary and wild-type.

Degradation treatments: their mechanism is based on the elimination of TTR amyloid fibrillins. Among them, we have doxycycline, tauroursodeoxycholic acid and green tea. There are no clinical trials that demonstrate the benefit of any of them, and only small observational studies have reported improvement in parameters such as strain or left ventricular mass.[120,121]

AL amiloidosis

Light chain amyloidosis (AL) is caused by a plasma cell dyscrasia, which produces the deposition of proteins derived from immunoglobulin light chain fragments.[110] Any type of plasma cell dyscrasia can lead to amyloidosis. This type of amyloidosis is systemic; therefore, the clinical manifestations are not specific and depend largely on the affected organs and tissues, such as proteinuria, generally in the nephrotic range, edema, hepatosplenomegaly, heart failure, carpal tunnel syndrome.[122-124] Light chain amyloidosis can also complicate other hemato-oncological diseases that produce monoclonal proteins, such as non-Hodgkin lymphoma (NHL) or chronic lymphocytic leukemia (CLL).[123,124] B-cell or plasma cell clonality can cause renal disease related to immunoglobulin production, even in the absence of direct tumor complications and without meeting current hematologic criteria for diagnosis and specific therapy, which has led to the concept of monoclonal gammopathy of renal significance (MGRS) and renal light chain amyloidosis.[125] In even rarer cases, the deposited amyloid material may come from immunoglobulin heavy chain fragments and, therefore, would be a heavy chain amyloidosis (AH).[126] The diagnosis of AL requires evidence of a monoclonal plasma cell proliferative

disorder. This may include: 1) Presence of a monoclonal protein in serum or urine on protein electrophoresis with immunofixation; 2) Abnormal serum free light chain ratio (Kappa/Lambda); 3) Plasmacytosis in the bone marrow (greater than or equal to 10% of plasma cells.[127,128] When light chain amyloidosis is diagnosed and criteria for multiple myeloma (MM) are also met, the diagnosis is most often simultaneous. It is much less common for MM to be diagnosed up to 6 or more months later after the initial diagnosis of light chain amyloidosis. This is called delayed progression.[129,130] It should be noted that light chain amyloidosis is not a diagnostic criterion for MM, however, patients with light chain amyloidosis without MM who have plasmacytosis in the bone marrow (plasma cells greater than or equal to 10%) should receive treatment similar to a patient diagnosed with MM.

Diagnostic criteria: the current diagnostic criteria for AL are based on those developed by the Mayo Clinic and the International Multiple Myeloma Working Group. All four of the following criteria must be met:[130,131]

1. Systemic syndrome related to the deposition of amyloid material: renal, hepatic, cardiac, gastrointestinal tract or peripheral nerve involvement.
2. Positive amyloid staining for Congo red in any tissue: fat aspirate, bone marrow, organ biopsy, or the presence of amyloid fibrils in electron microscopy.
3. Evidence that amyloid is light chain related, established by direct examination of amyloid using proteomic analysis based on immunoelectron spectrometry or microscopy.
4. Evidence of a monoclonal plasma cell proliferative disorder. (Monoclonal spike in protein electrophoresis with immunofixation in serum or urine, bone marrow plasmacytosis, altered Kappa/Lambda light chain ratio).

There is an increase in hemorrhagic complications in patients with amyloidosis. The etiology is often multifactorial, but three situations stand out that are directly related to amyloidosis: decreased activity of factor X, vascular infiltration with amyloid and decreased vitamin K-dependent factors, due to liver failure due to amyloid deposition in this organ and acquired von Willebrand disease (VWD). Clinically, a type of purpura and other skin manifestations (ecchymosis or petechiae) are observed, whose location is periorbital (raccoon eyes), although rare, it is very characteristic.[132] Other hemorrhagic manifestations may include a frank hemorrhagic diathesis with epistaxis, gingivorrhagia or gastrointestinal bleeding. A fourth pathogenetic mechanism of hemorrhagic manifestations, with normal coagulation tests, is the infiltration of the blood vessel walls by amyloid material.[133]

Treatment of light chain amyloidosis (AL), hematological approach

Once the diagnosis of AL is confirmed, the extent and sites of disease involvement must be established. A careful evaluation of comorbidities that may affect the intensity or density of the specific treatment (chemotherapy) must be made. It is highly recommended to have a complete medical history, a thorough physical examination and general laboratory studies. These include a complete blood count with differential, blood chemistry with liver function tests, serum electrolytes, 24-hour urine creatinine clearance, cardiac enzymes, brain natriuretic peptide, thyroid profile, prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT). In patients with bone marrow plasmacytosis (plasma cell count greater than or equal to 10%), the study protocol must be completed to confirm or rule out multiple myeloma or other plasma cell dyscrasias. The cytogenetic profile (t11;14, t4;14, t6;14, t14;16, t14;20, trisomy 1q+ 17p) and metastatic bone series[124,134,135] should be included.

The first step in treatment is to determine whether the patient is a candidate for hematopoietic cell transplantation (HCT). The eligibility criteria are identical for patients diagnosed with multiple myeloma.[136] If the patient is a candidate for HCT, this should be performed in a center with specific expertise in AL. If clinical trials are available, inclusion should be preferred. If not, remission

Table 12: Recommendations for modifying treatments.

Recommendation	Class of recommendation	Level of evidence
In patients with cardiac amyloidosis, the use of disease-modifying treatments is recommended	I	A
In patients with TTR amyloidosis (hereditary or wild-type) and functional class I-III, initiation of tafamidis should be considered	I	A
In patients with TTR amyloidosis (hereditary or wild-type) and functional class IV, initiation of tafamidis may be considered to improve quality of life	IIb	A
In patients with confirmed AL amyloidosis, the CyBorD regimen (Cyclophosphamide + Bortezomib + Dexamethasone) with or without daratumumab is recommended	I	A

AL = Light chains. TTR = Transthyretin.

induction therapy followed by high doses of melphalan and rescue with autologous HCT will be chosen. In case of an adequate response to induction, transplantation could be deferred, and a maintenance plan can be chosen. Regarding remission induction, the most recent data suggests the CyBorD regimen (Cyclophosphamide + Bortezomib + Dexamethasone) with daratumumab, as it has shown a better result in terms of depth of response. This same Dara-CyBorD regimen can be applied to those patients who are not candidates for HCT, evaluating the response cycle by cycle and assessing the addition of other chemotherapeutics[137] such as melphalan, venetoclax, ixazomib, bendamustine or immunomodulators such as thalidomide or lenalidomide, according to tolerance and toxicity (mainly neuropathy and myelotoxicity).

CyBorD Scheme:[138]

1. Bortezomib 1.3 to 1.5 mg/m^2 administered subcutaneously once a week.
2. Cyclophosphamide 500 mg (total dose) intravenously once a week.
3. Dexamethasone 20 to 40 mg orally once a week.

If available, and depending on the cardiac condition:

1. Daratumumab 1,800 mg IV or SC once weekly for cycles 1 and 2, then every 2 weeks until cycle 6, then monthly until progression. (FDA has not approved it for AL class IIIB or IV).
2. The expected hematologic responses are: 25% complete response, 60-65% partial and complete response. The median survival was 72 months overall and for the most advanced stages it was only 4 months *(Table 12)*.

After starting modifying treatment, the patient should be monitored in specialized clinics.

Cardiac transplantation

As we have mentioned, in the treatment of CA, 2 areas can be identified:

1. Treatment of comorbidities and prevention of complications and
2. The delay or stoppage of amyloid deposits through a specific treatment.

In the area of complications and comorbidities, there is the management of heart failure, arrhythmias, conduction disorders, prevention of thromboembolism and concomitant presence of severe aortic stenosis, among others.[139] Cardiac transplantation (CT) is an option that has grown in recent years.[140] The International Society for Heart and Lung Transplantation (ISHLT), in its latest report, specifies that only 3% of heart transplants were due to amyloidosis. Of those transplanted

due to restrictive cardiomyopathies (4,306 patients), 10.8% (466 patients) had a diagnosis of cardiac amyloidosis.[141] In our hospital, we have transplanted 2 cases of hereditary CA, with good results.

Cardiac amyloidosis due to AL

In these patients, cardiac transplantation was contraindicated. With better patient selection and advances in hematologic therapy for AL amyloidosis, the results have improved and are now comparable with those of non-amyloid etiology transplants. Generally, the treatment sequence used in patients with AL amyloidosis is as follows:

1. Suppression with chemotherapeutic agents.
2. Cardiac transplantation.
3. New suppressive therapy with chemotherapeutic agents followed by bone marrow transplantation.[139]

Transthyretin amyloidosis (ATTR)

TTR amyloidosis is a multisystem disease that predominantly affects the heart and nerves. In patients with end-stage heart failure due to ATTR, heart transplantation represents a treatment option provided there is no significant damage to other organs. Previous studies have shown conflicting results on whether heart transplantation in ATTR is associated with less favorable outcomes. Furthermore, given the progression of ATTR after heart transplantation, post-transplant management is controversial.[96,142]

Which patients are candidates for transplantation?

1. Transplantation in AL amyloidosis: following contemporary therapy, many centers may wait up to 1 year after chemotherapy treatment to consider cardiac transplantation candidates. Given the high risk of cardiovascular disease and mortality, patients with significant functional limitations and poor prognosis may be listed for transplantation, but if there is evidence of cardiac improvement, they should be removed from the list. This clinical improvement can be observed due to the reduction in natriuretic peptides, regression of cardiac amyloid after a one year of starting chemotherapy, normalization of light chain in serum, decreased need for loop diuretics, or improved functional capacity.[142,143]
   The 3 most important conditions for assessing the indication for transplantation in patients with AL amyloidosis are:
   a. Limited cardiac function despite medical treatment
   b. Adequate control of plasma cell dyscrasia and
   c. Absence of significant extra-cardiac disease (renal, pulmonary, hepatic and advanced peripheral or autonomic neuropathy).

2. Transplantation in TTR amyloidosis: in patients with TTR-CA undergoing CT, they are typically those with hereditary etiology, because in acquired or wild-type CA, the age of the patients is usually advanced.
   To consider a patient as a candidate for CT, the following should be considered:[28]
   a. Persistent symptoms despite optimal medical therapy, including Tafamidis (when available), adequate volume status, and need to taper or withdraw disease-modifying medications.
   b. Increase or persistence of NT-proBNP biomarkers, deterioration in echocardiogram and functional status (VO2peak), hospitalization for worsening HF or refractory ventricular arrhythmias.
   c. Absence of extra-cardiac involvement including severe peripheral neuropathy. Disabling neuropathy will not change after transplantation, so it can be considered a contraindication.

Thanks to current advances in treatment, combined with a multidisciplinary approach and careful selection, patients undergoing CT for amyloidosis can now have very favorable outcomes. Further studies will be needed to

evaluate the results of CT in patients with CA, now that several advances have been made in this pathology.

Cardiac rehabilitation

Considered within the broad spectrum of restrictive cardiomyopathies, where there is not always a notable decline in ventricular function, the physiological behavior of physical exercise in cardiac amyloidosis is usually comparable to that of heart failure with preserved ejection fraction. However, since the evidence in this field has been growing in recent years, allowing us to categorize this population, we have discovered some peculiarities inherent to this disease.

Cardiac rehabilitation (CR) is an interdisciplinary therapeutic intervention whose objective in patients with CA is not only to improve functional capacity, through the development of cardiorespiratory fitness (CRF), but also quality of life and its consequent long-term contributions, as has happened with patients most affected by heart failure. Particularly, however, we are faced with a multisystem storage disease, whose limitation will be primarily anatomical, but with the advantage of developing gains capable of solving the multi-pathological deficiencies that have been generated by the disease, especially the inability to increase stroke volume and cardiac output and the increase in biventricular filling pressures, in whose small-sized cavities, despite their preserved ejection fraction, is also aggravated by their usual chronotropic incompetence and deficient peripheral mechanisms.[144] Ultimately, exercise tolerance is a prognostic indicator in patients with transthyretin amyloidosis (ATTR), especially due to the gains associated with VO_2max and the joint action favored by the interdisciplinary nature of the program.[145]

Functional capacity assessment

Once the patient is compensated, the evaluation for admission to the CR program should be based on both the strict safety scrutiny of the program itself and on an exercise test for risk stratification and training prescription purposes. Strictly speaking, if the patient with ATTR CA is left to the natural evolution of the disease, even without changes in echocardiographic function, the CFR tends to worsen. The cardiopulmonary exercise test (CPET) is thus understood as the gold standard whose parameters mark the progression of the disease and guide the most specific treatment strategies for CR.[146]

While the advantages of the 6MW are its feasibility and reproducibility, and sometimes conventional exercise tests are a good attempt to assess risk and calculate a prescription zone, the CPET offers elements of great value in three areas of assessment:

1. Diagnosis: the recognition of CPET based on VO2peak as the main central diagnostic point is usually accompanied by the oxygen-pulse (O2-pulse) as a surrogate for stroke volume. In patients with CA, whether due to ATTR or light chains, it is also important to analyze ventilatory efficiency through the VE/VCO2 slope, whose high values of affectation have been attributed to excessive sympathetic-excitatory response and a high rate of physiological dead space during exercise, but also neurohumoral affectation typical of the disease.[147-149]
2. Prognosis: the dumbbell most associated with mortality is VO2peak with high VE/VCO2 slope.[150] The optimal threshold of percentage predicted of VO2peak for outcomes of < 62% (sensitivity 71% and specificity 68%, ABC 0.77, HF 0.65-0.88) in combination with > 3,000 pg proBNP-NT had a worse prognosis at 1 and 2 years with a survival of 69 ± 9% and 50 ± 10%, respectively.[151] Another combined risk marker consists of VO2peak of < 50% and forced vital capacity in pre-CPET baseline spirometry of < 70% with a high risk of mortality at 15 months (HR 26, HF 5-142).[152] In patients treated with tafamidis, low VO2peak, O2-pulse and circulatory power were associated with the primary endpoint of death, heart transplantation or initiation of palliative inotropic treatment (HR 0.43, 0.62 and 0.98, $p < 0.05$, respectively).[153]
3. Therapeutic prescription: based on the mechanisms of affectation detected during

the evaluation and the CPET, the specialist can address the needs of the patient with CA in relation to the presence or absence of ischemic threshold, dysautonomia. The specialist can also address the predominant mechanisms of dyspnea and the determination of exercise zones through ventilatory thresholds to define the exercise dose at which patients will be rehabilitated *(Table 13)*.

Characteristics of the physical training program and the interdisciplinary team

In any CR program, the suitability of the intervention requires concurrent treatment with moderate-intensity aerobic endurance training and muscle strength.[145] Evidence suggests that the most notable improvements in VO2peak and prognosis in patients with CA occur due to the benefits at the peripheral level, particularly in oxygen extraction with its consequent muscular use and its biological effects.[154,155] Therefore, strength training would seem to be the cornerstone of treatment. However, due to the central deficiencies of these patients in relation to cardiac output and index, and even more so in those with reduced LVEF, work on aerobic reserve should always be prioritized.[156] In order to follow the prescription model that guarantees sufficient training volume to produce adaptations in VO2peak - and therefore in the prognosis - it should be carried out under the conceptualization of HF, as proposed in *Table 6*.

It is important to assess whether there are symptoms associated with amyloid deposition in the autonomic nervous system or coronary circulation, with a component of orthostatic hypotension or with ischemic threshold, respectively. Based on this, training strategies for orthostatic challenge and ischemic threshold shift could be favorable in the care of these patients in CR.[157] Although patients with HF usually improve with high-intensity intervals, those with CA do not always tolerate high-intensity aerobic resistance loads, in which case the benefits of this strategy should be weighed against the risks on an individual basis.

Due to the lack of evidence, patients with CA and electrical alterations or elevated cardiac biomarkers should be compensated before entering a structured physical training program *(Table 14)*.

Attention to the psycho-emotional sphere is also essential not only for patients diagnosed with amyloidosis, but also to reduce the burden of mental illness on their caregivers. To this end, both individualized therapies and group interventions have shown to stabilize the emotional condition and reduce suicide rates, based primarily on changes in behavior regarding their illness and social reintegration *(Table 15)*.[145]

Table 13: Recommendations in measuring functional capacity.

Recommendation	Class of recommendation	Level of evidence
Any evaluation of a patient with CA for admission to a CR program should be accompanied by a supervised exercise test, ideally maximal and under the scrutiny of the competent specialist	IIA	A
The gold standard for measuring not only cardiorespiratory fitness but also the predominant causes of functional limitation on exertion is the cardiopulmonary exercise testing (CPET)	IIA	A
The 6-minute walk (6MW) can be used to measure functional capacity and elucidate limitation mechanisms in the absence of CPET	IIA	B
The CPET-derived prognostic markers with the greatest weight in risk stratification are predicted VO_2peak%, VE/VCO_2 slope and O_2-pulse, with some combined indicators of ventilation and pro-BNP	IIA	B

CA = Cardiac Amyloidosis. CPET = Cardiopulmonary Exercise Testing. CR = Cardiac Rehabilitation. pro-BNP = Pro-Brain Natriuretic Peptide. VE/VCO_2 = Ventilatory Equivalent for Carbon Dioxide. VO_2peak = Peak Oxygen Uptake.

Table 14: Generic recommendations for prescribing physical training in patients with cardiac amyloidosis.

Type of training	Frequency (per week)	Intensity (training load)	Session length (minutes)
Aerobic endurance	4-6	Moderate (70% of HRR)	20-40
Strength and physical qualities	3-5	Enough weight to achieve sets of 8-2 repetitions	30

HRR = Heart Rate Reserve.

PROGNOSIS

Knowing the prognosis factors of cardiac amyloidosis is crucial to guide the treatment of this disease. As we describe below, the type of amyloidosis and the cardiac involvement undoubtedly translate into prognosis.

Since the 1990's, it has been established that cardiac involvement in AL amyloidosis (immunoglobulin light chain amyloidosis) translates into a poor prognosis, which is further obscured by the diagnosis of heart failure with a survival of less than 1 year. Cardiac amyloidosis causes changes in the structure and function of the heart, which triggers heart failure, arrhythmias and restrictive cardiomyopathy.

Systematic reviews and meta-analyses have shown that age and gender have no implication in the prognosis. Below, we will describe the factors that do have prognostic implication.

Type of cardiac amyloidosis: Xin Y's meta-analysis, which brings together three publications with around 300 patients, shows that there are no significant differences in MACEs when comparing hATTR (hereditary transthyretin amyloidosis) and ATTRwt (wild-type transthyretin amyloidosis), while AL and TTR do show significant differences in MACEs and survival, with worse outcomes in AL.[158] When comparing TTR types, hATTR has a better survival prognosis and ATTRwt has a better prognosis in terms of MACEs.[40]

Hospitalizations for heart failure: patients with TTR amyloidosis have a higher number of hospitalizations for heart failure.[159] Regarding ATTRm variants of cardiac amyloidosis, the ATTR-ACT (Transthyretin Amyloidosis Cardiomyopathy Clinical Trial) analysis shows that patients with the hereditary amyloidosis variant p.Val142Ile had worse outcomes than ATTRwt patients.[36] It has also been reported that patients with V122I variants, which predominate in patients of African American descent, have a lower survival rate than the rest of the hereditary variants and wTTR.[160]

Echocardiogram: systolic function: the left ventricular ejection fraction (LVEF) has a positive correlation with the prognosis.[96] Undoubtedly, systolic dysfunction defines a late stage of the disease. A LVEF of less than 50% is associated with an increase in mortality.[161,162] Among the causes of death in patients with TTR cardiac amyloidosis, cardiovascular deaths predominate, and among these, heart failure is the protagonist or the main cause of cardiovascular deaths and hospitalizations.[163] The myocardial contraction fraction (MCF) that results from the relationship between stroke volume and myocardial volume is a prognostic marker of survival with a cut-off point of 25%. This is explained because when myocardial mass increases in patients with amyloidosis, there is a reduction in ventricular volumes and stroke volume, resulting in a decrease in MCF.[164] Under this same premise, a low stroke volume also predicts mortality with a cut-off point of 33 mL/m^2.[165]

Diastolic function: the evaluation of the filling pattern becomes important, since both the restrictive pattern and the thickness of the ventricular wall impact the prognosis of cardiac amyloidosis. To determine the restrictive pattern, the most useful parameter is the E/e', and the other parameter with prognostic implication is the deceleration time of the E wave.[158]

Imaging studies: in the nuclear medicine study with pyrophosphates (99mTc-PYP), a heart/contralateral hemithorax (H/CL) ratio of ≥ 1.6 and a magnetic resonance with late

enhancement with transmural gadolinium are data of poor prognosis.[166]

Biomarkers: there are scores that determine the stage of the disease and its prognosis. Most of these use biomarkers or combinations thereof. NT-proBNP has a positive correlation with poor prognosis.[158] If we combine a troponin T greater than 0.05 ng/mL and an NTproBNP of 3,000 pg/mL, we have an increase in mortality in stage III in patients with wild-type.[167] If we now combine the glomerular filtration rate of < 45 mL/min/1.73 m^2 with NT-proBNP of > 3,000 ng/L (stage III) in patients with hereditary or wild-type amyloidosis, survival decreases by up to 40 months compared to those in stage I. This was corroborated in 2018 with a cohort of around 800 patients.[168]

Glomerular filtration rate: in cardiac amyloidosis, it is a predictor of mortality.[158] A glomerular filtration rate of < 45 mL/min/1.73 m^2 is the cut-off point as an independent factor of mortality.[168]

Functional class: patients with impaired functional class, specifically NYHA III, have a two-year shorter survival rate than patients with functional class I and II. NYHA III is also an independent risk factor for cardiac arrhythmias, atrioventricular block, strokes, and hospitalizations for heart failure.[166]

Atrial fibrillation (AF): although no impact on patient survival has been demonstrated, the pathophysiology of AF makes the patient more susceptible to thromboembolism and diastolic dysfunction. AF has been associated with risk of heart failure and kidney disease.[166]

Stratification of cardiac amyloidosis: for light chain amyloidosis, the staging proposed by the Mayo Clinic includes the absolute difference in serum free light chain values, as well as NT-proBNP and troponin T values. Each variable is assigned a point with the following cut-off points: NT-proBNP of ≥ 1,800 pg/mL, troponin T of ≥ 0.025 ng/mL and free light chain difference of ≥ 18 mg/dL. The stages defined with these variables range from I to IV with a total of 0 to 3 points, respectively. Survival in stage I is 94 months, while in stage IV it is 5.8 months.[169]

NAC staging (National Amyloidosis Centre of the United Kingdom) is a staging proposed by Gillmore et al. and is defined as: stage I with NT-proBNP of ≤ 3,000 ng/L and a GFR of ≥ 45 mL/min; stage III, a value of NT-proBNP of >3000 ng/L and a GFR of < 45 mL/min; the rest are stage II.[168] Patients with NAC III with the established cut-off points of an NT-proBNP (3,000 ng/L) and GFR (45 mL/min) are a lower predictor of survival in all groups of cardiac

Table 15: Recommendations of intervention based on physical exercise.

Recommendation	Class of recommendation	Level of evidence
Structured, regular, supervised physical training is indicated in stable patients under CR guidelines for patients with HF	I	A
The recommendation for supervised training is concurrent (aerobic and strength) due to the known concomitant benefits of CPET	IIA	B
Training strategies for orthostatic challenge and management of the ischemic threshold are suggested in cases of dysautonomia or amyloid deposition in coronary arteries	IIA	B
Some patients may require a pacemaker to manage chronotropic incompetence associated with physical exercise[94]	IIA	B
There is no evidence on the recommendation of patients with CA to practice sports, either recreational or competitive	III	C
Nutrition strategies are essential to increase muscle mass and energy status during the day	IIA	A
The psycho-affective sphere should be treated in all patients with CA who enter the CR program to promote the patient's quality of life and reduce the social burden on the corresponding caregivers	IIA	B

CA = Cardiac Amyloidosis. CPET = Cardiopulmonary Exercise Testing. CR = Cardiac Rehabilitation. HF = Heart Failure.

Table 16: Prognosis factors.

Prognosis factor	Poor prognosis variable	Prognostic implication
Functional class NYHA	NYHA III	Lower survival. Independent risk factor for arrhythmias, hospitalization for heart failure and stroke
Heart (H)/contralateral hemithorax (CL) ratio	≥ 1.6	Poor prognosis
Troponin T	More than 0.05 ng/mL	Lower survival
NT-proBNP	> 3,000 ng/L	Lower survival
Myocardial contraction fraction	25%	Lower survival
Stroke volume	33 mL/m^2	Lower survival
Renal function	GFR of < 45 mL/min/1.73 m^2	Independent predictor of mortality
NAC scale	NAC III	Lower survival
Genetic variable in hereditary amyloidosis	V122I	Lower survival

NAC = National Amyloidosis Centre of the United Kingdom. NT-ProBNP = N-terminal Pro-Brain Natriuretic Peptide. NYHA = New York Heart Association. V122I = Valine 122 Isoleucine.

amyloidosis, decreasing survival from 5 to 2.5 years.[160]

Treatment: patients with and without treatment have a different prognosis. Treatment with Tafamidis has reduced cardiovascular death by 30% in TTR AL, as well as hospitalizations for heart failure by 35%. It is important to mention that this study included both types of TTR AL, however, 75% of the patients had TTRwt with a mean LVEF of 48% *(Table 16)*.[163]

GENETIC COUNSELING

Hereditary transthyretin amyloidosis (hATTR) is an autosomal dominant inherited genetic disease that presents a diagnostic challenge due to phenotypic variability due to variable expressivity and incomplete penetrance derived from the segregation of genetic variants belonging to certain geographic regions.[13,83,170] For this reason, an interdisciplinary approach that incorporates the assessment by specialists in Medical Genetics, as well as genetic counseling at each stage of the diagnosis, both clinical and molecular, is essential, as stipulated in clinical consensus.[83,170,171] Genetic counseling offers essential information about the mode of inheritance, recurrence risks, genetic testing, and other aspects related to the disease, providing tools for the patient and their family to make personal, reproductive, and medical decisions. Accurate diagnosis of hATTR requires molecular testing based on sequencing. Due to the nature of these tests and their possible results, it is necessary to perform pre-test and post-test genetic counseling so that the patient understands the scope, limitations, and possible implications. When a clinically actionable genetic variant in the TTR gene, pathogenic or likely pathogenic, is identified in an individual, it is important to identify other relatives at risk and carry out predictive or presymptomatic genetic testing (cascade testing), mainly in first-degree relatives.[170,171] The use of predictive genetic testing for the detection of hATTR-related variants in minors is controversial, as it is considered an adult-onset disease. However, each case must be individualized by evaluating the risk-benefit according to the evolution presented.[170,171]

CONCLUSIONS AND FUTURE PERSPECTIVES

Cardiac amyloidosis is a group of infiltrative diseases of different causes that frequently manifests as heart failure secondary to restrictive physiology. The diagnostic approach requires a high index of clinical suspicion and follow-up of structured diagnostic algorithms. The treatment of cardiomyopathy requires management of the congestive state of heart failure, the use of cardiac devices and anticoagulation in selected

cases. However, none of these treatments have demonstrated improved survival. Some disease-modifying treatments have demonstrated improved survival, so they should be considered as central therapy in patients with cardiac amyloidosis. Even with the advances that have been made in terms of diagnosis and treatment, more clinical trials of treatments are needed, as well as the development of earlier markers of cardiac amyloidosis. The challenges for patients continue to be delays in diagnosis, lack of specialized centers and access to treatments, so the dissemination and outreach regarding the teaching of cardiac amyloidosis should be considered a priority for our health system.

REFERENCES

1. 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 (14): 1357-1377.
2. 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. Circulation. 2020; 142 (1): e7-e22. doi: 10.1161/CIR.0000000000000792. Epub 2020 Jun 1. Erratum in: Circulation. 2021; 144 (1): e10. doi: 10.1161/CIR.0000000000000997. Erratum in: Circulation. 2021; 144 (1): e11.
3. Gertz MA, Dispenzieri A, Sher T. Pathophysiology and treatment of cardiac amyloidosis. Nat Rev Cardiol. 2015; 12 (2): 91-102. Available in: https://pubmed.ncbi.nlm.nih.gov/25311231/
4. Siddiqi OK, Ruberg FL. Cardiac amyloidosis: an update on pathophysiology, diagnosis, and treatment. Trends Cardiovasc Med. 2018; 28 (1): 10-21. Available in: https://pubmed.ncbi.nlm.nih.gov/28739313/
5. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med. 2018; 379 (11): 1007-1016. Available in: https://pubmed.ncbi.nlm.nih.gov/30145929/
6. Kyle RA, Larson DR, Kurtin PJ, Kumar S, Cerhan JR, Therneau TM et al. Incidence of AL amyloidosis in olmsted county, Minnesota, 1990 through 2015. Mayo Clin Proc. 2019; 94 (3): 465-471.
7. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. N Engl J Medi. 2003; 349 (6): 583-596. Available in: https://pubmed.ncbi.nlm.nih.gov/12904524/
8. Martinez-Naharro A, Hawkins PN, Fontana M. Cardiac amyloidosis. Clin Med (Lond). 2018; 18 (Suppl 2): s30-35. Available in: https://pubmed.ncbi.nlm.nih.gov/29700090/
9. Montserrat Moliner A, Waligora J. The European Union policy in the field of rare diseases. In: Advances in Experimental Medicine and Biology. Springer New York LLC; 2017. p. 561-587.
10. Aimo A, Merlo M, Porcari A, Georgiopoulos G, Pagura L, Vergaro G et al. Redefining the epidemiology of cardiac amyloidosis. A systematic review and meta-analysis of screening studies. Eur J Heart Fail. 2022; 24 (12): 2342-2351.
11. Ravichandran S, Lachmann HJ, Wechalekar AD. Epidemiologic and Survival Trends in Amyloidosis, 1987-2019. N Engl J Med. 2020; 382 (16): 1567-1568.
12. Cruz MW, Barroso F, González-Duarte A, Mundayat R, Ong ML; on behalf of the THAOS Investigators. The demographic, genetic, and clinical characteristics of Latin American subjects enrolled in the Transthyretin Amyloidosis Outcomes Survey. Amyloid. 2017; 24 (Sup1): 107-108.
13. González-Duarte A, Cárdenas-Soto K, Bañuelos CE, Fueyo O, Dominguez C, Torres B et al. Amyloidosis due to TTR mutations in Mexico with 4 distincts genotypes in the index cases. Orphanet J Rare Dis. 2018; 13 (1): 107.
14. Arshad S, Goldberg YH, Bhopalwala H, Dewaswala N, Miceli NS, Birks EJ et al. High prevalence of cardiac amyloidosis in clinically significant aortic stenosis: a meta-analysis. Cardiol Res. 2022; 13 (6): 357-371.
15. Magdi M, Mostafa MR, Abusnina W, Al-Abdouh A, Doss R, Mohamed S et al. A systematic review and meta-analysis of the prevalence of transthyretin amyloidosis in heart failure with preserved ejection fraction. Am J Cardiovasc Dis. 2022; 12 (3): 102-111. Available in: www.AJCD.us/
16. Kroi F, Fischer N, Gezin A, Hashim M, Rozenbaum MH. Estimating the gender distribution of patients with wild-type transthyretin amyloid cardiomyopathy: a systematic review and meta-analysis. Cardiol Ther. 2021; 10 (1): 41-55. Available in: https://doi.org/10.1007/s40119-
17. Nativi-Nicolau J, Siu A, Dispenzieri A, Maurer MS, Rapezzi C, Kristen AV et al. Temporal trends of wild-type transthyretin amyloid cardiomyopathy in the transthyretin amyloidosis outcomes survey. JACC CardioOncol. 2021; 3 (4): 537-546.
18. Pinney JH, Whelan CJ, Petrie A, Dungu J, Banypersad SM, Sattianayagam P et al. Senile systemic amyloidosis: clinical features at presentation and outcome. J Am Heart Assoc. 2013; 2 (2): e000098.
19. Wechalekar AD, Schonland SO, Kastritis E, Gillmore JD, Dimopoulos MA, Lane T et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Blood. 2013; 121 (17): 3420-3427. Available in: www.bloodjournal.org
20. Vaxman I, Gertz M. When to suspect a diagnosis of amyloidosis. Acta Haematol. 2020; 143 (4): 304-311.
21. Papa R, Lachmann HJ. Secondary, AA, Amyloidosis. Rheum Dis Clin North Am. 2018; 44 (4): 585-603.
22. Lachmann HJ, Goodman HJB, Gilbertson JA, Gallimore JR, Sabin CA, Gillmore JD et al. Natural history and outcome in systemic AA amyloidosis. N Engl J Med. 2007; 356 (23): 2361-2671. Available in: https://pubmed.ncbi.nlm.nih.gov/17554117/

23. Sattianayagam PT, Hawkins PN, Gillmore JD. Systemic amyloidosis and the gastrointestinal tract. Nat Rev Gastroenterol Hepatol. 2009; 6 (10): 608-617. Available in: https://pubmed.ncbi.nlm.nih.gov/19724253/
24. Fotiou D, Dimopoulos MA, Kastritis E. Systemic AL Amyloidosis: current approaches to diagnosis and management. Hemasphere. 2020; 4 (4): 12. Available in: /pmc/articles/PMC7430233/
25. Hwa YL, Fogaren T, Sams A, Faller DV, Stull DM, Thuenemann S et al. Immunoglobulin light-chain amyloidosis: clinical presentations and diagnostic approach. J Adv Pract Oncol. 2019; 10 (5): 470-481. Available in: /pmc/articles/PMC7779572/
26. Bird J. Guidelines on the diagnosis and management of AL amyloidosis. Br J Haematol. 2004; 125 (6): 681-700. Available in: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2141.2004.04970.x
27. Merlini G, Palladini G. Differential diagnosis of monoclonal gammopathy of undetermined significance. Hematology Am Soc Hematol Educ Program. 2012; 2012: 595-603. Available in: https://pubmed.ncbi.nlm.nih.gov/23233640/
28. Kittleson MM, Ruberg FL, Ambardekar A V., Brannagan TH, Cheng RK, Clarke JO et al. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: a report of the american college of cardiology solution set oversight committee. J Am Coll Cardiol. 2023; 81 (11): 1076-1126.
29. Nativi-Nicolau JN, Karam C, Khella S, Maurer MS. Screening for ATTR amyloidosis in the clinic: overlapping disorders, misdiagnosis, and multiorgan awareness. Heart Fail Rev. 2022; 27 (3): 785-793.
30. Tanskanen M, Peuralinna T, Polvikoski T, Notkola IL, Sulkava R, Hardy J et al. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: A population-based autopsy study. Ann Med. 2008; 40 (3): 232-239.
31. Sperry BW, Reyes BA, Ikram A, Donnelly JP, Phelan D, Jaber WA et al. Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release. J Am Coll Cardiol. 2018; 72 (17): 2040-2050.
32. González-López E, Gallego-Delgado M, Guzzo-Merello G, De Haro-Del Moral FJ, Cobo-Marcos M, Robles C et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J. 2015; 36 (38): 2585-2594.
33. 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 (8): e005066.
34. Castaño A, Bokhari S, Maurer MS. Unveiling wild-type transthyretin cardiac amyloidosis as a significant and potentially modifiable cause of heart failure with preserved ejection fraction. Eur Heart J. 2015; 36 (38): 2595-2597.
35. Eldhagen P, Berg S, Lund LH, Sorensson P, Suhr OB, Westermark P. Transthyretin amyloid deposits in lumbar spinal stenosis and assessment of signs of systemic amyloidosis. J Intern Med. 2021; 289 (6): 895-905.
36. Rapezzi C, Elliott P, Damy T, Nativi-Nicolau J, Berk JL, Velazquez EJ et al. Efficacy of tafamidis in patients with hereditary and wild-type transthyretin amyloid cardiomyopathy: further analyses from ATTR-ACT. JACC Heart Fail. 2021; 9 (2): 115-123.
37. 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 (4): 535-537. Available in: https://pubmed.ncbi.nlm.nih.gov/15695149/
38. 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 (7): 1089-1093. Available in: http://www.ajconline.org/article/S0002914914014544/fulltext
39. Abstract 16852: a simple voltage/mass index improves diagnosis of cardiac amyloidosis in patients with unexplained left ventricular "hypertrophy": an electrocardiographic and echocardiographic study of more than 500 patients | Circulation [Internet]. [cited 2024 Aug 22]. Available in: https://www.ahajournals.org/doi/10.1161/circ.122.suppl_21.A16852
40. Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O et al. Systemic cardiac amyloidoses: Disease profiles and clinical courses of the 3 main types. Circulation. 2009; 120 (13): 1203-1212.
41. Cheng Z, Kang L, Tian Z, Chen W, Guo W, Xu J et al Utility of combined indexes of electrocardiography and echocardiography in the diagnosis of biopsy proven primary cardiac amyloidosis. Ann Noninvasive Electrocardiol. 2011; 16 (1): 25-29.
42. Yilmaz A, Bauersachs J, Bengel F, Büchel R, Kindermann I, Klingel K et al. Diagnosis and treatment of cardiac amyloidosis: position statement of the German Cardiac Society (DGK). Clin Res Cardiol. 2021; 110 (4): 479-506. Available in: https://link.springer.com/article/10.1007/s00392-020-01799-3
43. Sperry BW, Vranian MN, Hachamovitch R, Joshi H, McCarthy M, Ikram A et al. Are classic predictors of voltage valid in cardiac amyloidosis? A contemporary analysis of electrocardiographic findings. Int J Cardiol. 2016; 214: 477-481. Available in: http://www.internationaljournalofcardiology.com/article/S0167527316307094/fulltext
44. Cappelli F, Vignini E, Martone R, Perlini S, Mussinelli R, Sabena A et al. Baseline ECG features and arrhythmic profile in transthyretin versus light chain cardiac amyloidosis. Circ Heart Fail. 2020; 13 (3): E006619. Available in: https://www.ahajournals.org/doi/10.1161/CIRCHEARTFAILURE.119.006619
45. Cipriani A, De Michieli L, Porcari A, Licchelli L, Sinigiani G, Tini G et al. Low QRS voltages in cardiac amyloidosis: clinical correlates and prognostic value. JACC CardioOncol. 2022; 4 (4): 458-470.
46. Mussinelli R, Salinaro F, Alogna A, Boldrini M, Raimondi A, Musca F et al. Diagnostic and prognostic value of low QRS voltages in cardiac AL amyloidosis. Ann Noninvasive Electrocardiol. 2013; 18 (3): 271-280.

47. Kristen A V., Perz JB, Schonland SO, Hegenbart U, Schnabel PA, Kristen JH et al. Non-invasive predictors of survival in cardiac amyloidosis. Eur J Heart Fail. 2007; 9 (6-7): 617-624. Available in: https://pubmed.ncbi.nlm.nih.gov/17350331/
48. Eriksson P, Karp K, Bjerle P, Olofsson BO. Disturbances of cardiac rhythm and conduction in familial amyloidosis with polyneuropathy. Heart. 1984; 51 (6): 658-662. Available in: https://heart.bmj.com/content/51/6/658
49. González-López E, Gagliardi C, Dominguez 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 (24): 1895-1904. Available in: https://pubmed.ncbi.nlm.nih.gov/28329248/
50. Hartnett J, Jaber W, Maurer M, Sperry B, Hanna M, Collier P et al. Electrophysiological manifestations of cardiac amyloidosis: JACC: CardioOncology State-of-the-Art Review. JACC Cardio Oncol. 2021; 3 (4): 506-515.
51. Reisinger J, Dubrey SW, Lavalley M, Skinner M, Falk RH. Electrophysiologic abnormalities in AL (Primary) amyloidosis with cardiac involvement. J Am Coll Cardiol. 1997; 30 (4): 1046-1051.
52. Dubrey SW, Cha K, Anderson J, Chamarthi B, Reisinger J, Skinner M et al. The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. QJM 1998; 91 (2): 141-157. Available in: https://dx.doi.org/10.1093/qjmed/91.2.141
53. Goldsmith YB, Liu J, Chou J, Hoffman J, Comenzo RL, Steingart RM. Frequencies and types of arrhythmias in patients with systemic light-chain amyloidosis with cardiac involvement undergoing stem cell transplantation on telemetry monitoring. Am J Cardiol. 2009; 104 (7): 990-994. Available in: http://www.ajconline.org/article/S0002914909011205/fulltext
54. Sharma S, Labib SB, Shah SP. Electrocardiogram criteria to diagnose cardiac amyloidosis in men with a bundle branch block. Am J Cardiol. 2021; 146: 89-94. Available in: http://www.ajconline.org/article/S0002914921000977/fulltext
55. Alreshq R, Tugal D, Siddiqi O, Ruberg F. Conduction abnormalities and role of cardiac pacing in cardiac amyloidosis: a systematic review. Pacing Clin Electrophysiol. 2021; 44 (12): 2092-2099. Available in: https://onlinelibrary.wiley.com/doi/full/10.1111/pace.14375
56. Barbhaiya CR, Kumar S, Baldinger SH, Michaud GF, Stevenson WG, Falk R et al. Electrophysiologic assessment of conduction abnormalities and atrial arrhythmias associated with amyloid cardiomyopathy. Heart Rhythm. 2016; 13 (2): 383-390. Available in: http://www.heartrhythmjournal.com/article/S1547527115011868/fulltext
57. Namdar M, Steffel J, Jetzer S, Schmied C, Hurlimann D, Camici GG et al. Value of electrocardiogram in the differentiation of hypertensive heart disease, hypertrophic cardiomyopathy, aortic stenosis, amyloidosis, and Fabry disease. Am J Cardiol. 2012; 109 (4): 587-593. Available in: http://www.ajconline.org/article/S0002914911030505/fulltext
58. Banypersad SM, Fontana M, Maestrini V, Sado DM, Captur G, Petrie A et al. T1 mapping and survival in systemic light-chain amyloidosis. Eur Heart J. 2015; 36 (4): 244-251.
59. Phelan D, Collier P, Thavendiranathan P, Popović ZB, Hanna M, Plana JC et al. 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 (19): 1442-1448.
60. Lee SP, Park JB, Kim HK, Kim YJ, Grogan M, Sohn DW. Contemporary imaging diagnosis of cardiac amyloidosis. J Cardiovasc Imaging. 2019; 27 (1): 1-10.
61. Roger-Rollé A, Cariou E, Rguez K, Fournier P, Lavie-Badie Y, Blanchard V et al. Toulouse amyloidosis research network collaborators. Can myocardial work indices contribute to the exploration of patients with cardiac amyloidosis? Open Heart. 2020; 7 (2): e001346.
62. Palmiero G, Rubino M, Monda E, Caiazza M, D'urso L, Carlomagno G et al. Global left ventricular myocardial work efficiency in heart failure patients with cardiac amyloidosis: pathophysiological implications and role in differential diagnosis. J Cardiovasc Echogr. 2021; 31 (3): 157. Available in: /pmc/articles/PMC8603776/
63. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA et al.. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: part 1 of 2-evidence base and standardized methods of imaging. J Nucl Cardiol. 2019; 26 (6): 2065-2123. doi: 10.1007/s12350-019-01760-6. Erratum in: J Nucl Cardiol. 2021; 28 (4): 1761-1762.
64. 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 (1): 1-10. Available in: https://bmccardiovascdisord.biomedcentral.com/articles/10.1186/s12872-016-0311-6
65. Syed IS, Glockner JF, Feng DL, Araoz PA, Martinez MW, Edwards WD et al. Role of cardiac magnetic resonance imaging in the detection of cardiac amyloidosis. JACC Cardiovasc Imaging. 2010; 3 (2): 155-164. Available in: https://pubmed.ncbi.nlm.nih.gov/20159642/
66. Carvalho FP de, Erthal F, Azevedo CF. The role of cardiac MR imaging in the assessment of patients with cardiac amyloidosis. Magn Reson Imaging Clin N Am. 2019; 27 (3): 453-463. Available in: https://pubmed.ncbi.nlm.nih.gov/31279449/
67. Yamaguchi S, Oda S, Kidoh M, Hayashi H, Takashio S, Usuku H et al. Cardiac MRI T1 and T2 mapping as a quantitative imaging biomarker in transthyretin amyloid cardiomyopathy. Acad Radiol. 2024; 31 (2): 514-522.
68. Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS et al. Magnetic resonance in transthyretin cardiac amyloidosis. J Am Coll Cardiol. 2017; 70 (4): 466-477. Available in: https://pubmed.ncbi.nlm.nih.gov/28728692/
69. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA et al. ASNC/AHA/ASE/EANM/HFSA/ISA/

SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: Part 1 of 2-evidence base and standardized methods of imaging. J Nucl Cardiol. 2019; 26 (6): 2065-2123. doi: 10.1007/s12350-019-01760-6. Erratum in: J Nucl Cardiol. 2021; 28 (4): 1761-1762.
70. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: part 1 of 2-evidence base and standardized methods of imaging. Circ Cardiovasc Imaging. 2021; 14 (7): e000029. Available in: https://doi.org/10.1161/HCI.0000000000000029
71. Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M et al. Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis. Circ Heart Fail. 2019; 12 (9): e006075.
72. Waheed A, Dorbala S. Current Status of Radionuclide Imaging of Transthyretin Cardiac Amyloidosis. Cardiol Clin. 2023; 41 (2): 217-231.
73. Meristoudis G, Ilias I, Keramida G. Potential diagnostic pitfalls of bone scintigraphy in transthyretin-related amyloidosis. World J Nucl Med. 2020; 19 (03): 313-314.
74. Saad JM, Ahmed AI, Han Y, Saeed S, Pournazari P, Al-Mallah MH. 99mTechnetium-labeled cardiac scintigraphy for suspected amyloidosis: a review of current and future directions. Heart Fail Rev. 2022; 27 (5): 1493-1503.
75. Embry-Dierson M, Farrell MB, Schockling E, Warren J, Jerome S. Cardiac amyloidosis imaging, part 1: amyloidosis etiology and image acquisition. J Nucl Med Technol. 2023; 51 (2): 83-89.
76. Schockling EJ, Farrell MB, Embry-Dierson M, Warren J, Jerome S. Cardiac amyloidosis imaging, part 2: quantification and technical considerations. J Nucl Med Technol. 2023; 51 (2): 90-98.
77. Dorbala S, Cuddy S, Falk RH. How to Image Cardiac Amyloidosis: A Practical Approach. JACC Cardiovasc Imaging. 2020; 13 (6): 1368-1383.
78. Jerome S, Farrell MB, Warren J, Embry-Dierson M, Schockling EJ. Cardiac amyloidosis imaging, part 3: interpretation, diagnosis, and treatment. J Nucl Med Technol. 2023; 51 (2): 102-116.
79. Joseph V, Julien HM, Bravo PE. Radionuclide imaging of cardiac amyloidosis. Vol. 16, PET Clinics. W.B. Saunders; 2021. p. 285-293.
80. Khor YM, Cuddy SAM, Singh V, Falk RH, Di Carli MF, Dorbala S. 99mTc bone-avid tracer cardiac scintigraphy: role in noninvasive diagnosis of transthyretin cardiac amyloidosis. Radiology. 2023; 306 (2): e221082.
81. Poterucha TJ, Elias P, Bokhari S, Einstein AJ, DeLuca A, Kinkhabwala M et al. Diagnosing transthyretin cardiac amyloidosis by technetium Tc 99m pyrophosphate: a test in evolution. JACC Cardiovasc Imaging. 2021; 14 (6): 1221-1231.
82. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the esc working group on myocardial and pericardial diseases. Eur Heart J. 2021; 42 (16): 1554-1568.
83. Brito D, Albrecht FC, de Arenaza DP, Bart N, Better N, Carvajal-Juarez I et al. World Heart Federation Consensus on Transthyretin Amyloidosis Cardiomyopathy (ATTR-CM). Glob Heart. 2023; 18 (1): 59.
84. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation. 2016; 133 (24): 2404-2412.
85. Witteles RM, Bokhari S, Damy T, Elliott PM, Falk RH, Fine NM et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. JACC Heart Fail. 2019; 7 (8): 709-716.
86. Wang CC, Chang WT, Lin YH, Tzeng BH, Chao TH, Hung CL et al. 2023 expert consensus of the taiwan society of cardiology on the diagnosis and treatment of cardiac amyloidosis. Acta Cardiol Sin. 2023; 39 (4): 511-543.
87. Papathanasiou M, Carpinteiro A, Rischpler C, Hagenacker T, Rassaf T, Luedike P. Diagnosing cardiac amyloidosis in every-day practice: a practical guide for the cardiologist. Vol. 28, IJC Heart and Vasculature. Elsevier Ireland Ltd; 2020.
88. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Vol. 118, Cardiovascular Research. Oxford University Press; 2022. p. 3272-3287.
89. Ruiz-Hueso R, Salamanca-Bautista P, Quesada-Simón MA, Yun S, Conde-Martel A, Morales-Rull JL et al. Estimating the prevalence of cardiac amyloidosis in old patients with heart failure-barriers and opportunities for improvement: The PREVAMIC Study. J Clin Med. 2023; 12 (6): 2273.
90. Gilstrap LG, Dominici F, Wang Y, El-Sady MS, Singh A, Di Carli MF et al. Epidemiology of cardiac amyloidosis–associated heart failure hospitalizations among fee-for-service medicare beneficiaries in the United States. Circ Heart Fail. 2019; 12 (6): e005407.
91. Banypersad SM, Moon JC, Whelan C, Hawkins PN, Wechalekar AD. Updates in cardiac amyloidosis: a review. J Am Heart Assoc. 2012; 1 (2): e000364.
92. Griffin JM, Maurer MS. Transthyretin cardiac amyloidosis: a treatable form of heart failure with a preserved ejection fraction. Trends Cardiovasc Med. 2021; 31 (1): 59-66.
93. Dobner S, Bernhard B, Asatryan B, Windecker S, Stortecky S, Pilgrim T et al. SGLT2 inhibitor therapy for transthyretin amyloid cardiomyopathy: early tolerance and clinical response to dapagliflozin. ESC Heart Fail. 2023; 10 (1): 397-404.
94. Porcari A, Cappelli F, Nitsche C, Tomasoni D, Sinigiani G, Longhi S et al. SGLT2 inhibitor therapy in patients with transthyretin amyloid cardiomyopathy. J Am Coll Cardiol. 2024; 83 (24): 2411-2422. Available in: https://pubmed.ncbi.nlm.nih.gov/38866445/
95. Donnelly JP, Hanna M. Cardiac amyloidosis: An update on diagnosis and treatment. Cleve Clin J Med. 2017; 84: 12-26.
96. Griffin JM, Rosenthal JL, Grodin JL, Maurer MS, Grogan M, Cheng RK. ATTR amyloidosis: current and emerging management strategies: JACC:

CardioOncology State-of-the-Art Review. JACC Cardio Oncol. 2021; 3 (4): 488-505.
97. Giancaterino S, Urey MA, Darden D, Hsu JC. Management of Arrhythmias in Cardiac Amyloidosis. JACC Clin Electrophysiol. 2020; 6 (4): 351-361.
98. Feng DL, Syed IS, Martinez M, Oh JK, Jaffe AS, Grogan M et al. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. Circulation. 2009; 119 (18): 2490-2497.
99. Dubrey S, Pollak A, Skinner M, Falk RH. Atrial thrombi occurring during sinus rhythm in cardiac amyloidosis: evidence for atrial electromechanical dissociation. Br Heart J. 1995; 74 (5): 541-544. Available in: http://heart.bmj.com/
100. Bukhari S, Khan SZ, Bashir Z. Atrial fibrillation, thromboembolic risk, and anticoagulation in cardiac amyloidosis: a review. J Card Fail. 2023; 29 (1): 76-86.
101. Donnellan E, Wazni O, Kanj M, Elshazly MB, Hussein A, Baranowski B et al. Atrial fibrillation ablation in patients with transthyretin cardiac amyloidosis. Europace. 2020; 22 (2): 259-264.
102. Vilches S, Fontana M, Gonzalez-Lopez E, Mitrani L, Saturi G, Renju M et al. Systemic embolism in amyloid transthyretin cardiomyopathy. Eur J Heart Fail. 2022; 24 (8): 1387-1396.
103. Bukhari S, Barakat AF, Eisele YS, Nieves R, Jain S, Saba S, Follansbee WP, Brownell A, Soman P. Prevalence of atrial fibrillation and thromboembolic risk in wild-type transthyretin amyloid cardiomyopathy. Circulation. 2021; 143 (13): 1335-1337.
104. Cappelli F, Tini G, Russo D, Emdin M, Del Franco A, Vergaro G et al. Arterial thrombo-embolic events in cardiac amyloidosis: a look beyond atrial fibrillation. Amyloid. 2021; 28 (1): 12-18.
105. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022; 145 (18): e895-e1032.
106. Mitrani LR, De Los Santos J, Driggin E, Kogan R, Helmke S, Goldsmith J et al. Anticoagulation with warfarin compared to novel oral anticoagulants for atrial fibrillation in adults with transthyretin cardiac amyloidosis: comparison of thromboembolic events and major bleeding. Amyloid. 2021; 28 (1): 30-34.
107. Laptseva N, Rossi VA, Sudano I, Schwotzer R, Ruschitzka F, Flammer AJ, Duru F. Arrhythmic manifestations of cardiac amyloidosis: challenges in risk stratification and clinical management. J Clin Med. 2023; 12 (7): 2581.
108. Kim EJ, Holmes BB, Huang S, Lugo R, Aboud A Al, Goodman S et al. Outcomes in patients with cardiac amyloidosis and implantable cardioverter-defibrillator. Europace. 2020; 22 (8): 1216-1223.
109. John RM. Arrhythmias in cardiac amyloidosis. J Innov Card Rhythm Manag. 2018; 9 (3): 3051-3057.
110. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary. Circulation. 2018; 138 (13): e210-271.
111. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Arbelo E, Barriales-Villa R et al. 2023 ESC Guidelines for the management of cardiomyopathies: Developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC). Eur Heart J. 2023; 44 (37): 3503-3626.
112. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022; 43 (40): 3997-4126.
113. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J. 2021; 42 (35): 3427-3520.
114. Cheung CC, Roston TM, Andrade JG, Bennett MT, Davis MK. Arrhythmias in cardiac amyloidosis: challenges in risk stratification and treatment. Can J Cardiol. 2020; 36 (3): 416-423.
115. Maurer MS, Kale P, Fontana M, Berk JL, Grogan M, Gustafsson F et al. Patisiran treatment in patients with transthyretin cardiac amyloidosis. N Engl J Med. 2023; 389 (17): 1553-1565. Available in: https://www.nejm.org/doi/full/10.1056/NEJMoa2300757
116. Siddiqi OK, Mints YY, Berk JL, Connors L, Doros G, Gopal DM et al. Diflunisal treatment is associated with improved survival for patients with early stage wild-type transthyretin (ATTR) amyloid cardiomyopathy: the Boston University Amyloidosis Center experience. Amyloid. 2022; 29 (2): 71-78. Available in: https://pubmed.ncbi.nlm.nih.gov/35083944/
117. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med. 2018; 379 (11): 1007-1016. Available in: https://www.nejm.org/doi/full/10.1056/NEJMoa1805689
118. Damy T, Garcia-Pavia P, Hanna M, Judge DP, Merlini G, Gundapaneni B et al. Efficacy and safety of tafamidis doses in the tafamidis in transthyretin cardiomyopathy clinical trial (ATTR-ACT) and long-term extension study. Eur J Heart Fail. 2021; 23 (2): 277-285. Available in: https://pubmed.ncbi.nlm.nih.gov/33070419/
119. Gillmore JD, Judge DP, Cappelli F, Fontana M, Garcia-Pavia P, Gibbs S et al. Efficacy and safety of acoramidis in transthyretin amyloid cardiomyopathy. N Engl J Med. 2024; 390 (2): 132-142. Available in: https://www.nejm.org/doi/full/10.1056/NEJMoa2305434
120. Karlstedt E, Jimenez-Zepeda V, Howlett JG, White JA, Fine NM. Clinical experience with the use of doxycycline and ursodeoxycholic acid for the treatment of transthyretin cardiac amyloidosis. J Card Fail. 2019; 25 (3): 147-153. Available in: https://pubmed.ncbi.nlm.nih.gov/30660664/
121. Aus dem Siepen F, Bauer R, Aurich M, Buss SJ, Steen H, Altland K et al. Green tea extract as a treatment for patients with wild-type transthyretin amyloidosis: an observational study. Drug Des Devel Ther. 2015; 9: 6319-6325. Available in: https://www.dovepress.com/green-tea-extract-as-a-treatment-for-patients-with-wild-type-transthyr-peer-reviewed-fulltext-article-DDDT

122. Macedo AVS, Schwartzmann PV, de Gusmao BM, Melo MDT, Coelho-Filho OR. Advances in the treatment of cardiac amyloidosis. Curr Treat Options Oncol. 2020; 21 (5): 36.
123. Milani P, Merlini G, Palladini G. Light chain amyloidosis. Mediterr J Hematol Infect Dis. 2018; 10 (1): e2018022
124. Palladini G, Schönland S, Merlini G, Milani P, Jaccard A, Bridoux F et al. The management of light chain (AL) amyloidosis in Europe: clinical characteristics, treatment patterns, and efficacy outcomes between 2004 and 2018. Blood Cancer J. 2023; 13 (1): 19.
125. Leung N, Bridoux F, Nasr SH. Monoclonal gammopathy of renal significance. N Engl J Med. 2021; 384 (20): 1931-1941.
126. Oe Y, Soma J, Sato H, Ito S. Heavy chain deposition disease: an overview. Clin Exp Nephrol. 2013; 17 (6): 771-778.
127. Ihne S, Morbach C, Obici L, Palladini G, Stork S. Amyloidosis in Heart Failure. Curr Heart Fail Rep. 2019; 16 (6): 285-303.
128. Palladini G, Russo P, Bosoni T, Verga L, Sarais G, Lavatelli F et al. Identification of amyloidogenic light chains requires the combination of serum-free light chain assay with immunofixation of serum and urine. Clin Chem. 2009; 55 (3): 499-504.
129. Madan S, Dispenzieri A, Lacy MQ, Buadi F, Hayman SR, Zeldenrust SR et al. Clinical features and treatment response of light chain (AL) amyloidosis diagnosed in patients with previous diagnosis of multiple myeloma. Mayo Clin Proc. 2010; 85 (3): 232-238.
130. Rajkumar SV, Gertz MA, Kyle RA. Primary systemic amyloidosis with delayed progression to multiple myeloma. Cancer. 1998; 82 (8): 1501-1505.
131. Rajkumar SV. Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol. 2016; 91 (7): 719-734.
132. Eder L, Bitterman H. Image in clinical medicine. Amyloid purpura. N Engl J Med. 2007; 356 (23): 2406. Available in: www.nejm.org
133. Mumford AD, O'Donnell J, Gillmore JD, Manning RA, Hawkins PN, Laffan M. Bleeding symptoms and coagulation abnormalities in 337 patients with AL-amyloidosis. Br J Haematol. 2000; 110 (2): 454-460.
134. Bochtler T, Hegenbart U, Kunz C, Granzow M, Benner A, Seckinger A et al. Translocation t(11;14) is associated with adverse outcome in patients with newly diagnosed AL amyloidosis when treated with bortezomib-based regimens. J Clin Oncol. 2015; 33 (12): 1371-1378.
135. Kastritis E, Palladini G, Minnema MC, Wechalekar AD, Jaccard A, Lee HC et al. Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis. N Engl J Med. 2021; 385 (1): 46-58.
136. Merlini G, Dispenzieri A, Sanchorawala V, Schönland SO, Palladini G, Hawkins PN, Gertz MA. Systemic immunoglobulin light chain amyloidosis. Nat Rev Dis Primers. 2018; 4 (1): 38.
137. Bhutani D, Lentzsch S. Diagnosis and management of systemic light chain AL amyloidosis. Pharmacol Ther. 2020; 214: 107612.
138. Manwani R, Cohen O, Sharpley F, Mahmood S, Sachchithanantham S, Foard D et al. A prospective observational study of 915 patients with systemic AL amyloidosis treated with upfront bortezomib. Blood. 2019; 134 (25): 2271-2280.
139. Decotto S, Villanueva E, Pérez de Arenaza D, Nucifora EM, Aguirre MA, Posadas-Martínez ML et al. Heart transplantation in amyloidosis. Clinical and imaging manifestations. Arch Cardiol Mex. 2022; 92 (3): 320-326.
140. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update. J Heart Lung Transplant. 2016; 35 (1): 1-23.
141. Hsich E, Singh TP, Cherikh WS, Harhay MO, Hayes D Jr, Perch M et al. The International thoracic organ transplant registry of the international society for heart and lung transplantation: Thirty-ninth adult heart transplantation report-2022; focus on transplant for restrictive heart disease. J Heart Lung Transplant. 2022; 41 (10): 1366-1375.
142. Sousa M, Monohan G, Rajagopalan N, Grigorian A, Guglin M. Heart transplantation in cardiac amyloidosis. Heart Fail Rev. 2017; 22 (3): 317-327.
143. Davis MK, Kale P, Liedtke M, Schrier S, Arai S, Wheeler M et al. Outcomes after heart transplantation for amyloid cardiomyopathy in the modern era. Am J Transplant. 2015; 15 (3): 650-658.
144. Vilas-Boas MDC, Rocha AP, Cardoso MN, Fernandes JM, Coelho T, Cunha JPS. Clinical 3-D Gait assessment of patients with polyneuropathy associated with hereditary transthyretin amyloidosis. Front Neurol. 2020; 11: 605282.
145. Dasgupta NR. Care of patients with transthyretin amyloidosis: the roles of nutrition, supplements, exercise, and mental health. Am J Cardiol. 2022; 185: S35-42.
146. Argirò A, Silverii MV, Burgisser C, Fattirolli F, Baldasseroni S, di Mario C et al. Serial changes in cardiopulmonary exercise testing parameters in untreated patients with transthyretin cardiac amyloidosis. Can J Cardiol. 2024; 40 (3): 364-369.
147. Banydeen R, Monfort A, Inamo J, Neviere R. Diagnostic and prognostic values of cardiopulmonary exercise testing in cardiac amyloidosis. Front Cardiovasc Med. 2022; 9: 898033.
148. Bartolini S, Baldasseroni S, Fattirolli F, Silverii MV, Piccioli L, Perfetto F et al. Poor right ventricular function is associated with impaired exercise capacity and ventilatory efficiency in transthyretin cardiac amyloid patients. Intern Emerg Med. 2021; 16 (3): 653-660.
149. Yunis A, Doros G, Luptak I, Connors LH, Sam F. Use of ventilatory efficiency slope as a marker for increased mortality in wild-type transthyretin cardiac amyloidosis. American Journal of Cardiology. 2019; 124 (1): 122-130.
150. Cantone A, Serenelli M, Sanguettoli F, Maio D, Fabbri G, Dal Passo B et al. Cardiopulmonary exercise testing predicts prognosis in amyloid cardiomyopathy: a systematic review and meta-analysis. ESC Heart Fail. 2023; 10 (4): 2740-2744.
151. Silverii MV, Argirò A, Baldasseroni S, Fumagalli C, Zampieri M, Guerrieri L et al. Prognostic value of

cardiopulmonary exercise testing in patients with transthyretin cardiac amyloidosis. Intern Emerg Med. 2023; 18 (2): 585-593.
152. Banydeen R, Eggleston R, Deney A, Monfort A, Ryu JH, Vergaro G et al. Risk stratification in transthyretin cardiac amyloidosis: the added value of lung spirometry. J Clin Med. 2023; 12 (11): 3684.
153. Dalia T, Acharya P, Chan WC, Sauer AJ, Weidling R, Fritzlen J et al. Prognostic role of cardiopulmonary exercise testing in wild-type transthyretin amyloid cardiomyopathy patients treated with tafamidis. J Card Fail. 2021; 27 (11): 1285-1289.
154. Swank AM, Horton J, Fleg JL, Fonarow GC, Keteyian S, Goldberg L et al. Modest increase in peak vo2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. Circ Heart Fail. 2012; 5 (5): 579-585.
155. Dhakal BP, Malhotra R, Murphy RM, Pappagianopoulos PP, Baggish AL, Weiner RB et al. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. Circ Heart Fail. 2015; 8 (2): 286-294.
156. Clemmensen TS, Soerensen J, Hansson NH, Tolbod LP, Harms HJ, Eiskjaer H et al. Myocardial oxygen consumption and efficiency in patients with cardiac amyloidosis. J Am Heart Assoc. 2018; 7 (21): e009974.
157. Rapezzi C, Milandri A, Lorenzini M. The complex interplay between systolic and diastolic function at rest and during exercise in heart failure: the case of cardiac amyloidosis. Eur J Heart Fail. 2017; 19 (11): 1466-1467.
158. Xin Y, Hu W, Chen X, Hu J, Sun Y, Zhao Y. Prognostic impact of light-chain and transthyretin-related categories in cardiac amyloidosis: a systematic review and meta-analysis. Hellenic J Cardiol. 2019; 60 (6): 375-383.
159. Nakahashi T, Arita T, Yamaji K, Inoue K, Yokota T, Hoshii Y et al. Impact of clinical and echocardiographic characteristics on occurrence of cardiac events in cardiac amyloidosis as proven by endomyocardial biopsy. Int J Cardiol. 2014; 176 (3): 753-759.
160. Lane T, Fontana M, Martinez-Naharro A, Quarta CC, Whelan CJ, Petrie A et al. Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis. Circulation. 2019; 140 (1): 16-26.
161. Bhuiyan T, Helmke S, Patel AR, Ruberg FL, Packman J, Cheung K et al. Pressure-volume relationships in patients with transthyretin (ATTR) cardiac amyloidosis secondary to V122i mutations and wild-type transthyretin transthyretin cardiac amyloid study (TRACS). Circ Heart Fail. 2011; 4 (2): 121-128.
162. Ruberg FL, Maurer MS, Judge DP, Zeldenrust S, Skinner M, Kim AY et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the transthyretin amyloidosis cardiac study (TRACS). Am Heart J. 2012; 164 (2): 222-228.e1.
163. Miller AB, Januzzi JL, O'Neill BJ, Gundapaneni B, Patterson TA, Sultan MB et al. Causes of cardiovascular hospitalization and death in patients with transthyretin amyloid cardiomyopathy (from the tafamidis in transthyretin cardiomyopathy clinical trial [ATTR-ACT]). Am J Cardiol. 2021; 148: 146-150.
164. Rubin J, Steidley DE, Carlsson M, Ong Mohlim, Maurer MS. Myocardial contraction fraction by M-mode echocardiography is superior to ejection fraction in predicting mortality in transthyretin amyloidosis. J Card Fail. 2018; 24 (8): 504-511.
165. Milani P, Dispenzieri A, Scott CG, Gertz MA, Perlini S, Mussinelli R et al. Independent prognostic value of stroke volume index in patients with immunoglobulin light chain amyloidosis. Circ Cardiovasc Imaging. 2018; 11 (5): e006588.
166. Feng KY, Loungani RS, Rao VN, Patel CB, Khouri MG, Felker GM, DeVore AD. Best practices for prognostic evaluation of a patient with transthyretin amyloid cardiomyopathy. JACC CardioOncol. 2019; 1 (2): 273-279.
167. 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 (10): 1014-1020.
168. Gillmore JD, Damy T, Fontana M, Hutchinson M, Lachmann HJ, Martinez-Naharro A et al. A new staging system for cardiac transthyretin amyloidosis. Eur Heart J. 2018; 39 (30): 2799-2806. Available in: https://pubmed.ncbi.nlm.nih.gov/29048471/
169. Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol. 2012; 30 (9): 989-995.
170. Gillmore JD, Reilly MM, Coats CJ, Cooper R, Cox H, Coyne MRE et al. Clinical and genetic evaluation of people with or at risk of hereditary ATTR Amyloidosis: an expert opinion and consensus on best practice in ireland and the UK. Adv Ther. 2022; 39 (6): 2292-2301. Available in: https://pubmed.ncbi.nlm.nih.gov/35419651/
171. Grandis M, Obici L, Luigetti M, Briani C, Benedicenti F, Bisogni G et al. Recommendations for pre-symptomatic genetic testing for hereditary transthyretin amyloidosis in the era of effective therapy: a multicenter Italian consensus. Orphanet J Rare Dis. 2020; 15 (1): 348. Available in: /pmc/articles/PMC7734774/
172. Pagourelias ED, Mirea O, Duchenne J, Van Cleemput J, et al. Echo Parameters for Differential Diagnosis in Cardiac Amyloidosis: A Head-to-Head Comparison of Deformation and Nondeformation Parameters. Circ Cardiovasc Imaging. 2017 Mar;10(3):e005588.

Correspondence:
José Ángel Cigarroa López
E-mail: drangelcigarroa@gmail.com

Enrique Alexander Berrios Bárcenas
E-mail: enrique.berrios@cardiologia.org